THE RECOGNITION OF ATROPHIC GASTRITIS

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I declare that this thesis has been composed by myself and that the work described is my own except where otherwise stated.

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CONTENTS

PREFACE

The origins, nature and significance of atrophic gastritis are ill understood despite the common occurrence of the condition and the researches of many investigators during the past century.

The subject of this thesis is a study in depth of the condition as found in a small group of patients, of its relationship to other pathological processes, its influence upon gastric function and of methods whereby its presence may be detected.

SUMMARY

The historical aspects of atrophic gastritis have been reviewed as has the evidence for the various theories as to the aetiology of the condition. The association between atrophic gastritis and the anaemias, its relationship to gastric cancer, and its significance as a disease entity have been discussed, and a fourfold rationale for the importance of recognising the condition have been advanced in the light of these associations.

Multiple gastric biopsy was carried out upon one hundred and eleven patients over the age of forty years who were under investigation for dyspeptic symptoms. The overall incidence of atrophic gastritis was 64%, being highest in those with gastric cancer and lowest in those with duodenal ulceration. Intestinal metaplasia of the gastric mucosa was found only in those with atrophic gastritis but was not confined to those with severe atrophic changes. No aspects of the clinical history or findings pointed to specific diagnostic features, but a significantly high incidence of gastric cancer was found in the family history of those with atrophic gastritis.

The intramuscular pentagastrin test was evaluated by comparison with other tests of gastric secretion, and when employed in the patients under study was found to discriminate between those with atrophic and those with normal mucosa with an accuracy of 81%. The value of radiology, gastroscopy and blind gastric photography in the recognition of atrophic gastritis was studied. Discrimination between atrophic and normal gastric mucosa was accurate in 68% by barium meal examination, 65% by gastroscopy and 53% by gastric photography.

The haematological status of the subjects was studied, and a

significantly high incidence of anaemia, but not of iron deficiency, was found among those with atrophic gastritis. Low serum Vitamin B_{12} levels were found in 8%, and parietal cell antibodies in 17% of those with atrophic gastritis, and in none with normal mucosa, while the incidence of thyroid antibodies was higher in those with atrophic changes, but not significantly so. An increase in the incidence of blood group A was found in those with atrophic gastritis when compared with those with normal mucosa and with a comparable contrast group.

Gastric emptying rates were studied using a radioactive labelled meal and were found to be significantly slower in subjects with atrophic gastritis and with gastric cancer when compared with a healthy contrast group of subjects. The significance of this finding has been discussed.

The value and reliability of the clinical and haematological investigations in the detection of atrophic gastritis have been discussed, and an overall diagnostic accuracy of 89% with a false-positive incidence of 3% found, when the combined results were analysed.

CHAPTER 1

INTRODUCTION

The concept of chronic inflammation of the stomach dates back for many centuries, but one of the earliest descriptions was that of Broussais (1831). While serving as a surgeon in Napoleon Boneparte's army he studied and reported on the existence of chronic 'inflammations' of the gastric lining, observed at autopsy on casualties in the Napoleonic wars. He and many other earlier writers based their observations and conclusions upon the examination of the gastric mucosa taken often many hours after death when post-mortem autolysis had become established, and their description, often of gross widespread lesions, led to misconception and confusion until the early part of the present century. In 1854 Handfield Jones observed and reported upon his finding of atrophy of the gastric mucosa in a patient dying from anaemia, and Fenwick (1870) described with clarity the gastric mucosa of a patient dying of 'Addisonian idiopathic anaemia' as showing a state of atrophy of 'the whole glandular portion of the organ'. In 1900, Faber and Bloch, dissatisfied with the difficulties imposed by post-mortem changes in the stomach, injected formalin into the organ immediately after death and were able to provide a meaningful and accurate description of the morphological appearances of the gastric mucosa in pernicious anaemia.

With the advent of modern surgery in the first four decades of this century, descriptions of the gastric mucosa, normal and abnormal, were derived from operation specimens. Descriptions of gastritis in its varying forms by Saltzmann (1913), Hurst and Venables (1929), Faber (1935) and Konjetzny (1938), served to establish the condition as an entity and pointed to a relationship between gastritis and gastric cancer. Despite the painstaking care and accuracy with which these and other workers described their findings, their specimens were obtained either at operation on stomachs the seat of disease, or at

autopsy. A further criticism, levelled by Schindler, Necheles and Gold (1939), lay in the fact that mucosal erosions could readily occur during gastric resection, which could invalidate many of the descriptions of mucosal abnormalities found in gastrectomy specimens.

Gastric biopsy was first reported by Chevalier Jackson in 1907 to the New York Academy of Medicine (Jackson, 1907). This procedure was carried out using a hollow-ended gastroscope, the specimen being obtained using a grab forcep. This technique was principally used for the histological examination of ulcers, tumours and polyps and he considered the taking of biopsy specimens from flat mucosa or ulcers to be unjustifiably hazardous. Gastric biopsy under direct vision was also practised by Kenamore (1940) and Benedict (1948) using a Schindler flexible gastroscope, and by Williams, Truelove, Gear, Massarella and Fitzgerald (1968), using a flexible fibreoptic gastroscope designed for this purpose by the Japanese. While specimens of gastric mucosa were obtained by these investigators, the method was primarily used for the gastroscopic visualisation and biopsy of discrete lesions of the stomach.

For the study of the gastric mucosa in health and for the evaluation of diffuse lesions of stomach, a simpler method of biopsy was required which would not have the limitations and risks of morbidity, inevitably associated with gastroscopy.

In 1894 the condition of 'erosive gastritis' was described by Einhorn (Einhorn, 1894) from a study of fragments of mucosa aspirated by a stomach tube. Originally considered to be fragments of desquamated epithelium, Hawksley and Cooray (1948) considered the possibility that this finding might be the result of aspiration of hitherto intact mucosa. Similar fragments were noted by Wood in 1948 (Wood, quoted by Joske Finckh and Wood, 1955) and this provided the stimulus which led

to the design of a simple suction biopsy tube for blind gastric biopsy. In 1949, Wood and his co-workers (Wood, Doig, Motteram and Hughes, 1949) published a description of such an instrument with a preliminary report upon a small number of biopsies taken with it. The instrument consisted of a steel cylinder 3 cm in length and of 6 mm diameter with a 3 mm open port on one side. Contained within the cylinder was a cylindrical knife attached to a pull-wire encased in a sealed length of Bowden cable. When the tube was swallowed, suction applied at the proximal end of the instrument allowed a knuckle of mucosa to be sucked in to the side hole in the cylinder (or 'capsule') which was then cut off by pulling upon the wire connected to the knife. This instrument, being small, was easy to swallow, could be used without the need for any elaborate preparation as an outpatient procedure, and with negligible risk of complications or morbidity. The development of this simple instrument opened the door to the possibility of obtaining specimens of gastric mucosa safely and easily and without the disadvantages of the previous methods, which have already been outlined. Many different models of biopsy tube of varying complexity have been developed since the original 'Wood' tube (Tomenius, 1950; Palmer, 1950; Rubin, Goldgraber and Smith, 1953; Shiner, 1956; Crosby and Kugler, 1957; Brandborg, Rubin and Quinton, 1959; Flick, Quinton and Rubin, 1961; Sielaff, 1961; Quinton, Flick and Rubin, 1962), but all share the principle of suction biopsy with a small easily swallowed tube, and their use has resulted in a large literature on the morphology of the gastric mucosa in health and disease. Not only has a clear picture emerged of the histological appearances of the normal stomach and of the diffuse lesions to which the organ is subject, but understanding of the relationship of gastric mucosal abnormalities to other disease processes has been substantially

advanced as a direct result of the development of this method of investigation.

CHAPTER 2

CHRONIC ATROPHIC GASTRITIS

1. Definition

The features of chronic gastritis affecting the mucosa of the body of the stomach have been described by numerous authors, notably Faber (1935), Doig (1949), Motteram (1951), Doig and Wood (1952), Magnus (1952), Joske, Finckh and Wood (1955), Wood and Taft (1958) and Bock, Richards and Witts (1963). The histological appearances present a continuous spectrum, ranging from minimal variations from the normal to complete gastric atrophy. Classifications of differing complexity have been advanced by these and other authors but essentially four main types of gastritis may be recognised:

(i) Superficial gastritis, in which there is chronic inflammation limited to the superficial layers of the lamina propria which may be of varying grades of severity. Some writers, notably Williams, Edwards, Lewis and Coghill (1957) and Motteram (1951), regard atrophy of the superficially placed glands as a feature of superficial gastritis, while Wood and Taft (1958), and Siurala, Isokoski, Varis and Kekki (1968) would regard the presence of atrophy as indicative of atrophic gastritis. In the elaborate description of Joske, Finckh and Wood, differentiation is made between superficial gastritis with and without atrophy. Such differences of interpretation have led to much confusion in the interpretation of the literature and in comparisons between different series, and this problem will be discussed further in a subsequent chapter.

(ii) Atrophic gastritis, which presents as a diffuse inflammation of the full thickness of the mucosa, with varying degrees of atrophy of the specific secretory cells.

(iii) Gastric atrophy, in which atrophy of the specific cells is complete and inflammation inconspicuous.

In addition to these features, intestinal metaplasia is not infrequently found as part of the picture of atrophic gastritis. In this condition, gastric epithelium is patchily replaced by an epithelium which has the morphological and staining properties of intestinal mucosa, with columnar cells, goblet and argentaffin cells, and Paneth cells in the bases of the crypts of Lieberkühn.

(iv) Diffuse giant hypertrophic gastritis, or Menetrier's disease (Menetrier, 1888) is a rare condition which may diffusely involve the mucosa or be more localised, and in which there is a benign hyperplasia of the surface epithelium with elongation and branching of the pits and infiltration of the lamina propria with inflammatory cells. It is included for completeness among the chronic gastritides but will not be discussed further as it is a separate disease entity and not related to chronic atrophic gastritis.

2. Incidence

The incidence of atrophic gastritis in the population is unknown. Of all the published studies on the findings resulting from gastric biopsy, all but one relate to selected groups of subjects, either persons being investigated for gastro-duodenal disorders, or selected age groups. The one exception to this is a random study conducted by Siurala and his co-workers (1968) on a Finnish rural population. Of 1046 people examined, 147 were randomly selected for gastric biopsy, this being successfully accomplished in 142 with an age range of from 16 to 65 years. Forty-seven per cent had normal gastric mucosa, 25% superficial gastritis and 28% atrophic gastritis. Intestinal metaplasia was found in 42% of those with gastritis. The incidence of atrophic gastritis increased with age, from 6% in those under 20 years of age to 60% in those over 60 years, and the incidence

of intestinal metaplasia followed a similar pattern. There was no significant difference in the incidence between the sexes.

In studies each of 1000 consecutive gastric biopsies on selected patients undergoing gastro-intestinal investigation, Joske Finckh and Wood (1955) and Williams, Edwards, Lewis and Coghill (1957) reported an incidence of 40% and 28% respectively and also found a steady increase with age in the incidence of atrophic gastritis, and are in agreement with Siurala's finding that no significant sex difference existed. Valencia-Parpacen and Pomer (1965) in a further 1000 gastric biopsies, found evidence of gastritis in 25% of cases selected from hospital patients, but only a quarter of those were defined as atrophic gastritis, the remainder showing the features of superficial gastritis. In common with the previously quoted authors, they found no sex difference in the incidence, but found no evidence that the incidence increased with age. This view is shared by Palmer (1952 and 1954) who failed to find any evidence of gastritis in 30 asymptomatic patients over the age of 60, but is at variance with the findings of Andrews, Haneman, Arnold, Booth and Taylor (1968) who found atrophic gastritis in all but one of 24 asymptomatic subjects over the age of 64 years.

3. Aetiology

Many opinions have been advanced as to the aetiology of chronic atrophic gastritis. The condition is known to be related to age but not to sex (Guiss and Stewart, 1943; Hebbel, 1943; Doig and Wood, 1952; Williams, Edwards, Lewis and Coghill, 1957; Siurala and Vuorinen, 1963; Edwards and Coghill, 1966), but no other definite causative factors have been established.

The place of trauma has been considered from various aspects

by a number of authors. Morson (1962) in discussing intestinal metaplasia points out that, as this is a feature of gastritis, a common aetiological background is to be expected. He stresses the situation in the stomach where the highest incidence of intestinal metaplasia is found as being the 'Magenstrasse', the lesser curvature of the body and pyloric antrum, and considers that the trauma of food passing across this area may play a part in the genesis of chronic gastritis. Reflux of bile causing gastritis by irritation and mucosal damage has been cited by Lawson (1964) and Butler and Buckler (1966) as a factor, especially in connection with the gastric stump following gastric resection where atrophic gastritis is a frequent finding (Witts, 1966). Chronic gastritis often accompanies gastric ulceration (Magnus, 1937), and Du Plessis (1965) and Capper (1967) have advanced the view that bile reflux plays a major aetiological role in the genesis of this condition. Doig, Funder and Weiden (1951), Brown and Wood (1955), Levin, Chapman, Palmer and Kirsner (1957), have reported upon the development of atrophic gastritis following X-irradiation of the stomach for peptic ulcer and the last-named authors have shown a correlation between the severity of the changes and increasing irradiation dosage. Ischaemia, produced by arterial ligation in the rat, leads to the development of atrophic gastritis (Leese, 1968), and Sommers (1958) has produced similar changes by the application of methylcholanthrene to the gastric mucosa in the experimental animal.

The place of diet has been investigated by a number of authors. Palmer (1954) held the view that alcohol, while a cause of acute gastritis, did not result in atrophic gastritis but Joske, Finckh and Wood (1955) considered, and produced evidence to show, that there was a high incidence of chronic gastritis in alcoholics. Edwards and Coghill (1966) in a careful study showed that the incidence of

gastritis was higher in heavy drinkers than in non-drinkers and that this finding was independent of age. They also showed that heavy smoking bore a similar relation to the incidence of atrophic gastritis. Edwards and Edwards (1956) showed that an association existed between the drinking of hot tea and the incidence of gastritis, and Edwards and Coghill (1966) elaborating upon this noted that this relationship was independent of age and social class. Unspecified dietary factors may play a part in the association between social class and gastritis, the highest incidence of which was in the lower classes, IV and V (Coghill and Edwards, 1966). A similar pattern exists in the incidence of gastric carcinoma in England and Wales, Norway, the U.S.A. and Denmark (Doll, 1956) and it is tempting to correlate these two findings in the light of the well-recognised association between the two conditions. Dietary factors have been implicated in relation to differences in the racial incidence of gastric cancer and enormous scope exists for large and prospective studies on the incidence of atrophic gastritis in relation to environmental and dietary factors.

The adult form of pernicious anaemia is invariably accompanied by atrophic gastritis or gastric atrophy (Faber and Bloch, 1900; Magnus and Ungley, 1938). While gastric atrophy was regarded for many years as the lesion of pernicious anaemia, it is now well-recognised that atrophic gastritis is, if anything, a more common finding in this condition, and that gastric atrophy may be found unassociated with pernicious anaemia (Joske, Finckh and Wood, 1955). It now seems unlikely that there are two distinct types of gastric lesion in pernicious anaemia, the one an atrophic gastritis of varying severity and the other a primary gastric atrophy, and it is generally believed that these are successive stages of the same disease (Magnus, 1958). There are many cases in which achlorhydria has been discovered up to

twenty years before the development of pernicious anaemia (Witts, 1966), and Siurala, Varis and Wiljasalo (1966) in a prolonged follow-up of patients with atrophic gastritis noted a progression in the severity of gastritis, with the development of pernicious anaemia in one case and latent pernicious anaemia in a further 7 of 60 patients re-examined after 15 years. The paucity of documented evidence of a transition from simple atrophic gastritis to pernicious anaemia indicates, however, that this is not a common occurrence.

In the past ten years, several lines of investigation have contributed evidence suggesting that chronic atrophic gastritis, including the gastric lesion of pernicious anaemia, is an organ specific autoimmune disease, comparable with autoimmune thyroiditis. Taylor (1959) first suggested that an autoantibody to intrinsic factor might be present in pernicious anaemia and Jeffries, Hoskins and Sleisenger (1962) developed a test which depended upon the capacity of intrinsic factor (I.F.) antibody to combine with and alter the electrophoretic mobility of Vitamin B_{12} - I.F. complex. Using this test Taylor (1962) demonstrated the antibody in the sera of 40% of pernicious anaemia patients. Roitt, Doniach and Shapland (1962) showed that two antibodies to I.F. exist, one reacting with the Vitamin B_{12} binding site on the intrinsic factor molecule, and the other with a distant site. In 1962, Markson, and Moore, Irvine, Davies, Delamore and Williams, and Taylor, Roitt, Doniach, Couchman and Shapland showed that an antibody in the serum of patients suffering from pernicious anaemia reacted with preparations of acid-secreting gastric mucosa, using a complement fixation test. This antibody, a globulin, was a cellular 'microsomal' constituent and was shown to react specifically with the cytoplasm of gastric parietal cells when a fluorescent antibody technique was employed (Taylor et al., 1962).

This latter technique has proved more sensitive than complement fixation and Taylor (1965), and Coghill, Doniach, Roitt, Mollin and Wynn Williams (1965) have found parietal cell antibody to be present in 86 and 89 per cent respectively of cases of pernicious anaemia. This antibody was present in 50 and 61 per cent respectively of patients with chronic atrophic gastritis, and in 8 and 9 per cent respectively of matched normal control subjects. Intrinsic factor antibody was not found in any case who did not have pernicious anaemia. The latter authors found some correlation between the degree of atrophy and incidence of parietal cell antibody but no correlation between the presence of antibody and the degree of small cell infiltrate or intestinal metaplasia of the gastric mucosa. The incidence of parietal cell antibody was very much higher in females than in males and was usually associated with iron deficiency anaemia. This latter association was taken a step further by Shearman, Delamore and Gardner (1966) who showed that parietal cell antibody was associated with chronic atrophic gastritis in the presence of idiopathic iron deficiency anaemia, but not with anaemia associated with chronic blood loss in which atrophic gastritis was less severe and achlorhydria less frequent.

It has been shown that chronic thyroiditis and pernicious anaemia co-exist more commonly than by chance (Williams and Doniach, 1962) as do thyrotoxicosis and pernicious anaemia (Doniach and Roitt, 1964). Similar associations have been shown between chronic atrophic gastritis without pernicious anaemia and primary hypothyroidism (Irvine, Davies, Delamore and Williams, 1962), and thyrotoxicosis (Siurala and Lomberg, 1959; Williams and Blair, 1964). These associations are accompanied by an overlap in the occurrence of gastric and thyroid autoantibodies, 40% of gastritic patients having

both thyroid and parietal cell antibodies (Coghill, Doniach, Roitt, Mollin and Williams, 1965), and 59% of pernicious anaemia patients having thyroid autoantibodies (Taylor, 1965). These and other workers have shown that gastric and thyroid autoantibodies are organ specific and the association between them suggests a common aetiological factor.

There is evidence of genetic factors being involved in the occurrence of autoimmune thyroiditis (Hall, Owen and Smart, 1960) and of pernicious anaemia (Faber, 1935; Callender and Denborough, 1957), and Oliver and Wilkinson (1933) showed that achlorhydria had a tendency to run in families. Doniach and her co-workers (1964) showed that not only were there associations between the incidence of thyroid disorders and atrophic gastritis in patients themselves but they detected increased incidences of both thyroid and gastric antibodies in the relatives of patients with autoimmune thyroiditis and pernicious anaemia.

There is thus strong evidence of an autoimmune basis for atrophic gastritis though it is not clear why only a small proportion of these patients develop pernicious anaemia. Doniach and Roitt suggest that the development of autoimmunity to intrinsic factor may play the decisive role. That not all patients with atrophic gastritis show evidence of autoimmunity is also abundantly clear and Te Velde, Hoedemaeker, Anders, Arends and Niewig (1966) suggest that atrophic gastritis without parietal cell antibodies is a patchy lesion unlike the diffuse lesion of the body of the stomach found in the antibody positive subjects. While many problems remain to be solved, a proportion of patients with atrophic gastritis owe their pathology to an autoimmune process with a genetic background, both of which may play their part in determining the response of the gastric mucosa to the

many insults to which it is subjected over the course of the life of the individual.

An association between both Addison's disease and hypopituitarism and reduced gastric acid secretion has been recognised for a number of years. Addison (1855) described 'sickness, vomiting and pain' as features of the disorder which he attributed to acute gastric ulceration. Gray, Ramsay and Thorn (1956), however, were able to find evidence of chronic peptic ulceration in only 3 of 363 cases of Addison's disease collected from the literature, an incidence of less than 1% compared with the accepted incidence in the population of between 5 and 10 per cent (Ivy, Grossman and Bachrach, 1950; Doll and Jones, 1951). Hypochlorhydria or achlorhydria have been noted as features in patients with Addison's disease by a number of writers (Conybeare and Willis, 1924; Rowntree and Snell, 1931; Maranon, Sala and Arguelles, 1934), and Smith, Delamore and Williams (1961) found not only a reduced acid output but evidence of atrophic gastric mucosal changes on gastric biopsy in 8 out of 12 patients with the disease. In Cushing's syndrome gastric hypersecretion is often found and is restored to normal levels by subtotal adrenalectomy (Kyle, Logan, Neill and Welbourn, 1956). In normal subjects, injection of A.C.T.H. for several weeks has been shown by Gray (1959) to increase both the basal secretion of HCl and the acid response to histamine stimulation. In animal experiments conflicting findings have been reported but Crean (1963; 1965) found marked reduction in acid production following adrenalectomy; this observation was unaccompanied by any marked effect on the parietal cell mass of the rat. Mackintosh (1966), working with dogs, noted a significant suppression of acid secretion following the prolonged administration of the cortisol inhibitor Metyrapone; this was restored to normal levels by giving cortisol. He and other writers consider that cortisol

is essential to normal gastric secretion, this probably being due to an action on as yet unidentified enzyme systems in the parietal cell.

Attention has been recently focused upon the role of auto-antibodies in Addison's disease. Blizzard, Chandler, Kyle and Hung (1962) found adrenal antibodies in the serum of 16 of 30 patients; half of these patients also exhibited thyroid antibodies. Irvine (1963) found gastric and thyroid antibodies in addition to adrenal antibodies in a high proportion of patients with idiopathic adrenal insufficiency; achlorhydria was present in 7 out of 9 of these subjects, but the incidence was less in another group of patients with adrenal insufficiency due to either tuberculosis or hypopituitarism. Irvine suggested that idiopathic adrenal insufficiency was associated with a disorder of immunological tolerance and that its pathogenesis might be closely related to that of chronic thyroiditis and pernicious anaemia.

Snapper, Groen, Hunter and Witts (1937) noted hypochlorhydria in cases of hypopituitarism, an association subsequently recorded by Escamilla and Lisser (1942), Summers (1952), Card and Sircus (1958) and by Smith, Delamore and Williams (1961). Smith et al (1961) and Kyle (1955) carried out gastric biopsy on their subjects and found atrophic changes in the gastric mucosa. Spence and Witts (1939) treated a patient with hypopituitarism with thyrotropic and gonado-tropic extracts of the pituitary gland and observed a restoration of gastric secretion and apparent regeneration of the gastric mucosa consequent upon this treatment. Treatment with cortisone of such patients has not, however, been found to influence a return of gastric secretion (Card and Sircus, 1958; Smith et al., 1961). In experiments with rats, hypophysectomy produces a rapid and severe fall in gastric acid production with a reduction in the parietal cell population and

mass of the gastric mucosa (Baker and Clark, 1961; Crean, 1963, 1965). Crean showed that these changes were principally mediated by lack of growth hormone and that they could be reversed by replacement with a preparation of this hormone. Bilateral adrenalectomy, on the other hand, did not have any marked effect on the structure of the gastric mucosa, suggesting that the changes noted after hypophysectomy were unlikely to be mediated via the adrenal cortex.

It would thus appear that the functional capacity of the parietal cell is dependent upon adequate levels of circulating glucocorticoids, while its structure is dependent upon the integrity of the anterior pituitary mediated by growth hormone. In addition, in idiopathic adrenal insufficiency, an auto-immune component may act directly upon the parietal cell and may play a part in the hypochlorhydria and gastric atrophy found in these cases. The administration of glucocorticoids may therefore be of value in restoring acid secretion in adrenal insufficiency, by direct replacement at parietal cell level. They may also be active in suppressing antibody formation, permitting regeneration of parietal cells, as has been suggested in those cases of pernicious anaemia in whom an improvement of the anaemia and return of HCl and intrinsic factor secretion has followed the administration of prednisolone (Doig, Girdwood, Duthie and Knox, 1957; Jefferies, 1965). Prednisolone will not, however, restore the secretory capacity in hypopituitarism; in these cases growth hormone is required.

4. Associated conditions

(i) Gastric carcinoma It is a widely held view that an association exists between carcinoma of the stomach and chronic atrophic gastritis, and it is the opinion of many investigators

that atrophic gastritis may be considered to be a pre-cancerous condition. It was from this postulate that the investigation reported in this thesis had its origins, with a view to examining the evidence for such an association, and investigating methods for the recognition of atrophic gastritis.

Schindler (1947) stated in the opening paragraph of his monograph on gastritis that half the medical world denied the significance of gastritis, while the other half believed it to be the most important disease of the stomach. Hunt (1929) stated that chronic gastritis was found in at least 80% of cancerous stomachs, and Ringertz (1961) quotes Orator (1926) and Tuomikoski (1936) as having found a similar incidence of fundal chronic gastritis to be present in association with gastric cancer. Konjetzny (1936) from a large experience, stated that gastric cancer never arose in a stomach whose mucosa was hitherto normal, and cited evidence that chronic gastritis was invariably a feature of the mucosa of stomachs, the seat of malignant change. Schade (1958 and 1960), from cytological and histological studies in a large number of cases, states that carcinoma nearly always develops in a diseased gastric mucosa, and especially in association with atrophic gastritis which he believes to be the primary condition and not secondary to carcinomatous change. In a series of 100 cases of gastric carcinoma subjected to biopsy of

gastric body mucosa, only 2 had histologically normal mucosa, 72% having atrophic gastritis (Krenz, 1968). Further supporting evidence in favour of an association between gastric cancer and an atrophic mucosa comes from studies of the incidence of cancer in pernicious anaemia. Kaplan and Rigler (1945) in large autopsy series found the incidence of gastric cancer in patients with pernicious anaemia to be 12% and Mosbech and Videback (1950) found that 15 (13%) of 115 patients with pernicious anaemia had developed gastric carcinoma over a mean period of 10 years, an incidence in both series of over 3 times the expected incidence in a corresponding normal population. In statistical studies of mortality rates, Hitchcock, Sullivan and Wangensteen (1955), found that the incidence of gastric cancer in a group of 1747 patients from a Cancer Detection Clinic was 3.2 times the expected national incidence in achlorhydric subjects, and 18.3 times the national incidence in persons with pernicious anaemia. In a further study based on hospital records from the Mayo Clinic, Berkson and Comfort (1956) found the incidence of gastric cancer in patients with pernicious anaemia to be over 4 times the expected incidence of the population as a whole. The incidence of achlorhydria and hypochlorhydria in gastric carcinoma is at least 80% in most published series and will be discussed in a subsequent chapter, but this finding also lends support to the probability of cancer developing against the background of atrophic gastritis.

It may be argued that the common finding of atrophic changes in the stomach in the presence of carcinoma is simply a reflection of age, and Guiss and Stewart (1943) pointed out from autopsy evidence that 80% of stomachs in persons over the age of 40 had chronic atrophic gastritis compared with 97% in patients with gastric cancer. They held the view that age was the common factor and that

there was no proof of any causative or sequential relationship between the two conditions. It may also be argued that the apparent causative relationship between pernicious anaemia and gastric cancer may have another explanation. That a genetic basis exists for pernicious anaemia is well known (Witts, 1966). There is also evidence that genetic factors play a part in the genesis of gastric carcinoma. While racial differences are probably attributable to environmental factors (Doll, 1956), the preponderance of gastric cancer occurring in persons of Blood Group A has been recognised in England and Wales (Aird and Bentall, 1953) and there is evidence that the frequency of the disease in relatives of those with gastric cancer is about 4 times the expected incidence (Videback and Mosbech, 1954; Flood, 1958). It is possible, therefore, that these two conditions share a common genetic background and that atrophic gastritis, though a common factor, is aetiologically unimportant.

The existence of gastric mucosal atrophy preceding the development of carcinoma has been demonstrated in cases other than those with pernicious anaemia. Comfort, Kelsey and Berkson (1947) carried out a retrospective study of the results of gastric analysis in a group of patients carried out 2 or more years before they presented with gastric carcinoma. Achlorhydria had been present in 48% of these cases, an incidence significantly higher than would be expected in their age group, and suggestive of pre-existing atrophic gastritis. In a 15-year follow-up study with gastric biopsy, Siurala, Varis and Wiljasalo (1966) found that 9 (8%) of 115 subjects with atrophic gastritis had developed gastric cancer during the period, compared with none in a comparable control group with normal gastric mucosa. Further suggestive negative evidence exists in the well-recognised rarity of gastric cancer developing in patients with

duodenal ulcer in whom atrophic gastritis is least often found, and, when present, less extensive than in stomachs with benign or malignant gastric ulcer (Morson, 1955). Orringer (1950) reported the incidence of carcinoma developing in the presence of duodenal ulcer as 0.4% and Kirschenfeld, Mermelstein and Aronsen (1965), in reviewing the literature, were able to find records of only 14 cases among over 2500 patients with duodenal ulcer, an incidence of 0.5%.

The place of intestinal metaplasia of the gastric mucosa in the genesis of carcinoma of the stomach has excited considerable interest. Intestinal epithelium was first recognised in the stomach in 1883 by Küpffer, who considered it to be a congenital 'rest', and Magnus (1937) regarded it as a heterotopic epithelium arising from a predetermined stem cell in the gastric mucosa. It is now generally regarded to be the result of metaplasia, a transformation of gastric epithelium to one of intestinal type in response to chronic irritation. The microscopic feature which most distinguishes it is the goblet cell which contains mucin which stains blue with haematoxylin, or with Alcian blue and red with mucicarmine. Gastric mucus secreting cells do not have this staining property which is peculiar to intestinal mucus (Jarvi and Lauren, 1951). The other histological features of intestinal type gastric epithelium are discussed in a later chapter. Intestinal epithelium has been found in the foetal stomach (Salenius, 1962; Stemmerman, 1967) and its incidence increases with age (Stout, 1945; Morson, 1955). There is no difference in the incidence between males and females (Morson, 1955). Gastric intestinal mucosa is similar in many respects to the mucosa of the small intestine, structurally and histochemically. Electron microscopy has revealed a very close similarity between this aberrant epithelium and the epithelium of the normal jejunum (Rubin, Ross, Jeffries and Sleisenger, 1966) and cell

proliferation kinetic studies have shown that the aberrant epithelium proliferates at the same rate as does jejunal epithelium (Winawer and Lipkin, 1967) and significantly more rapidly than does normal gastric epithelium (Croft, Pollok and Coghill, 1966). Histochemical studies have revealed close similarities between several enzyme systems in gastric intestinal epithelium and normal intestinal epithelium. As well as the staining reactions of mucins already mentioned, a close parallel exists between amino-peptidase and alkaline phosphatase activity in the two epithelia (Wattenberg, 1959; Planteyd and Willighagen, 1960) and between the electrophoretic patterns of the lactic dehydrogenase and aldolase isoenzymes (Leese, 1965 and 1968). Finally, it has been demonstrated that not only is there a close structural and chemical similarity between these epithelia, but intestinal epithelium in the stomach is capable of incorporating and transporting dietary and micellar lipid (Rubin, Ross, Jeffries and Sleisenger, 1966) which is thus introduced into the lamina propria, and also of actively transporting glucose (Klein, Sleisenger and Weser, 1968).

In the adult, intestinal metaplasia is found only in association with atrophic gastritis and Magnus (1937) found it to be present in 74% of stomachs resected for gastric ulcer, 60% with carcinoma and 20% with duodenal ulcer. Morson (1955) found intestinal metaplasia in 92% of stomachs resected for cancer, 82% for gastric ulcer and 65% for duodenal ulcer. He found that not only was the incidence highest in stomachs exhibiting malignant change, but that the changes were most severe and most extensive in these cases, when compared with stomachs resected for gastric or duodenal ulceration. It is most often found in the pyloric antrum, the commonest site for carcinoma, but in pernicious anaemia, where carcinoma most commonly

affects the body of the stomach, the incidence of intestinal metaplasia is highest in this region (Schell, Docherty and Comfort, 1954; Zamcheck, Grable, Ley and Norman, 1955; Sirsat, 1967).

Gossett and Masson (1912) believed that some cases of gastric carcinoma arose from intestinalised gastric epithelium and Jarvi and Lauren (1951) and Mulligan and Rember (1954) found incidences of 30% and 25% respectively of intestinal cell carcinoma in their series of operation and autopsy specimens. Morson (1955 and 1962) found a similar incidence and now believes (1969) that at least 50% of gastric cancers originate in this way. Histochemical studies have confirmed close similarities between aminopeptidase and alkaline phosphatase patterns in many stomach cancers on the one hand, and intestinal epithelium on the other (Wattenberg, 1959; Planteydt and Willighagen, 1960; Stemmerman, 1967), and Leese (1965) has obtained similar findings with the lactic acid dehydrogenase isoenzymes. These patterns are entirely different from those found in normal gastric mucosa and strongly suggest an intestinal cell origin for a large proportion of gastric cancers.

A further important feature of the pre-cancerous potential of intestinal metaplasia is the demonstration of the high turnover of cells when compared with normal epithelium as judged by mitosis counts, and by the measurement of D.N.A. in the gastric washings of subjects with atrophic gastritis as compared with persons with normal gastric mucosa (Croft, Pollock and Coghill, 1966). A further point of interest is the demonstration of the capability of intestinalised gastric epithelium of transporting lipids into the lamina propria (Rubin, Ross, Jeffries and Sleisenger, 1966; Siurala and Tarpila, 1967) which may indicate a route whereby dietary carcinogens may gain access to the gastric mucosa.

(ii) Anaemia The associations between chronic atrophic gastritis and pernicious anaemia have already been discussed, but atrophic gastritis is also frequently associated with iron deficiency anaemia. Employing the Augmented Histamine Test, Callender, Retief and Witts (1960) found 16% of 70 patients with iron deficiency anaemia to be achlorhydric and an additional 7% hypochlorhydric, and similar findings were reported by Jacobs, Lawrie, Entwistle and Campbell (1966) after maximal stimulation with histamine by intravenous infusion. This increased incidence of low gastric acid output in iron deficiency is matched by a significantly increased incidence of gastritis in these subjects (Davidson and Markson, 1955; Badenoch, Evans and Richards, 1957; Ikkala and Siurala, 1964). These investigators, while finding good correlation between acid output and gastritis, did not, however, show any correlation between the severity of the anaemia and that of the gastritis.

Theories concerning the relationship between gastritis and iron deficiency anaemia fall into two broad groups. The first is that achlorhydria is one of several aetiological factors in the genesis of iron deficiency anaemia, while the second is that atrophic gastritis develops as a result of iron deficiency. In the first theory, it has been postulated that the achlorhydria is due to gastritis which gives rise to occult bleeding (Wood and Taft, 1958) though there is no direct evidence to support this. Occult bleeding is, however, not uncommon in iron deficiency anaemia (Bannerman, Beveridge and Witts, 1964) and this possibility cannot be excluded. It has for long been a matter of debate as to whether achlorhydria results in malabsorption of iron. It has been shown (Jacobs, Bothwell and Charlton, 1964) that the addition of HCl to a test dose of iron will increase the absorption of ferric chloride in achlorhydric subjects, but not that of bound haemoglobin iron. Isotopic studies (Goldberg, Lochead and Dagg, 1963)

have also revealed a reduction of iron absorption in the presence of achlorhydria. Jacobs (1967) showed that acid limited the polymerisation of iron in solution and prevented its becoming bound to protein, so that at a low pH it was in a reactive state and available for absorption in the small bowel. Jacobs and Miles (1969), taking this further, have shown that normal gastric juice contains non-protein constituents with which iron will combine at low pH, and will thereafter remain in a soluble form irrespective of pH and thus be available for intestinal absorption. Achlorhydria will therefore limit the formation of these soluble iron complexes, promote iron binding with large molecule protein fractions, and thus limit iron absorption.

Witts (1953 and 1956) postulated that iron deficiency may be a cause of gastritis and the resultant failure of gastric secretion. Since the introduction of accurate methods of estimating gastric acid output, several groups of workers have shown that in some cases with idiopathic iron deficiency anaemia and achlorhydria or hypochlorhydria, a rise in acid output may result from therapeutic repletion of iron stores (Delamore and Shearman, 1965; Jacobs, Lawrie, Entwistle and Campbell, 1966; Stone, 1968). One of the more constant findings in such studies has been the irreversibility of the gastric mucosal lesion, and Delamore and Shearman have suggested that the improvement in acid secretion may be due to repletion of iron-containing enzyme systems in the parietal cell. It is noteworthy that in all such studies, the majority of patients in whom acid output increased following upon the administration of iron were under 30 years of age and were not achlorhydric. This would support the theory of enzyme repletion in existing parietal cells, there being no evidence of the reappearance of parietal cells in those cases in whom severe atrophic gastritis is present (Desai, Mehta, Borkar and Jeejeebhoy, 1968).

The definition of 'idiopathic' iron deficiency anaemia is one which is difficult to apply, as although there may be no current evidence of blood loss or dietary deficiency, it is seldom possible to exclude this retrospectively. It may well be the case that both theories as to the relationship between iron deficiency anaemia and low acid secretion have application in many instances. Anaemia may develop from overt or occult blood loss, or from dietary deficiency, leading to hypo- or achlorhydria by virtue of depletion of iron-containing enzyme systems in the gastric mucosa. This, in turn, may result in iron malabsorption, thus preventing repletion of body iron from normal dietary intake. It is recognised that antibodies to parietal cells are present in the sera of certain patients with atrophic gastritis and low acid secretion, and that the incidence is highest in those with iron deficiency (Shearman, Delamore and Gardner, 1966). It has been suggested (Stone, 1968) that in certain individuals, genetic influences may determine the elaboration of parietal cell antibodies in response to the initial mucosal injury from the anaemia, and thus lead to a perpetuation of both atrophic gastritis and iron deficiency anaemia from diminished iron absorption. The incidence of parietal cell antibodies in association with atrophic gastritis has a highly significant preponderance in females (Doniach, Roitt, Mollin and Williams, 1965) and iron deficiency anaemia is likewise found more commonly in women than in men in a ratio of at least 4:1 (Jacobs, Kilpatrick and Withey, 1965). It is thus tempting to speculate upon the possibility of iron deficiency having an aetiological as well as a collateral relationship to atrophic gastritis.

Atrophic gastritis as a cause of dyspepsia

Wood and Taft (1958) described the symptoms of atrophic gastritis

as being distinctive and showing little variation from patient to patient. They found a female preponderance and described the symptoms as consisting of epigastric fullness or pain after meals. The symptoms were felt diffusely across the epigastrium in contrast to the localised pain of peptic ulcer, and occurred usually immediately after the taking of food. Exacerbations and remissions were common, as was anorexia and weight loss. The age of onset was in the mid-forties, like gastric ulcer and unlike duodenal ulcer. Joske, Finckh and Wood (1955) found that 40% of 221 cases of atrophic gastritis had symptoms due to this condition (but 37% had no symptoms). In a review of a series of 50 patients with non-ulcer dyspepsia Shiner and Doniach (1956) found that 18% had atrophic gastritis. They found no great difference between the symptomatology of those with atrophic gastritis and those with either normal mucosa and barium negative dyspepsia or peptic ulcer disease. In a similar study by Williams, Edwards, Lewis and Coghill (1957), atrophic gastritis was found in 14.5% of 200 cases of non-ulcer dyspepsia and they were unable to relate the gastric mucosal findings on biopsy to any definite pattern of symptomatology. It would thus appear that, while atrophic gastritis may give rise to symptoms, this is by no means invariable, and despite Wood and Taft's didactic statement, atrophic gastritis is not a condition that is likely to be recognised on symptomatological and physical findings alone.

The importance of recognising atrophic gastritis is therefore fourfold:

(i) As a possible pre-cancerous condition.

(ii) As a possible precursor of pernicious anaemia.

(iii) In view of its association with iron deficiency anaemia, especially in young people where correction of iron deficiency may arrest the progress of the condition.

(iv) As a cause of dyspepsia in the absence of radiological or other evidence of gross upper gastrointestinal disease.

CHAPTER 3

MATERIAL AND METHODS

Patients studied

One hundred and fifteen patients were studied, of whom 76 were male and 39 female. All were in the age range of between 40 and 77 years, 24 being between 40 and 50 years, 31 between 51 and 60 years, 30 between 61 and 70 years, and 29 over the age of 70 (Table I). All were hospital patients undergoing investigation for dyspeptic symptoms.

The diagnostic categories into which the patients fell are shown in Table II. The diagnosis of duodenal ulcer was made by barium meal examination, often confirmed at subsequent operation. In the case of gastric ulcer, the diagnosis was made on similar criteria, often supplemented by gastroscopy. Similar diagnostic criteria were used in the diagnosis of gastric carcinoma, which was confirmed histologically in all cases at either operation or autopsy. The term 'non-ulcer dyspepsia' was applied to those patients in whom clinical and radiological investigation, and often gastroscopy, had revealed no evidence of peptic ulcer disease or carcinoma of the stomach, or of any other gross lesion of the upper alimentary tract. The diagnosis of pernicious anaemia was made as a result of haematological investigation including the finding of a megaloblastic bone marrow. The majority of these patients were known cases of pernicious anaemia, under treatment at the time of the current investigation. They have been shown as a separate group on account of the singularity of their pathology, but in certain sections of the study they are included amongst those exhibiting the features of atrophic gastritis or gastric atrophy.

No normal subjects were included in this particular investigation, as it was not considered ethically justifiable to subject such individuals to the extensive investigations which were included in

Age range	Male	Female	Total
40 - 50 yr.	20	4	24
51 - 60 yr.	21	10	31
61 - 70 yr.	19	11	30
over 70 yr.	16	14	30
Total	76	39	115

Table I: The age and sex distribution of the patients studied.

Diagnosis	Male	Female	Total
Non ulcer dyspepsia	20	20	40
Duodenal ulcer	20	2	22
Gastric ulcer	17	4	21
Gastric carcinoma	13	10	23
Pernicious anaemia	6	3	9
	76	39	115

Table II: The sex and diagnosis of the patients studied.

the major portion of the study. Normal subject volunteers were, however, included in certain sections of the study and will be referred to in subsequent chapters.

Method of investigation

Each patient was investigated as an in-patient, either in a general surgical ward, or in the Tenovus clinical research unit in Cardiff Royal Infirmary. Patients were referred either from the Surgical Unit outpatient clinic or from other surgical or medical units or the Department of Diagnostic Radiology of the United Cardiff Hospitals.

The study consisted of the following series of investigations:

(a) History of present complaint; past medical history; family history with especial reference to cancer, anaemia and goitre; social history and place of origin.

(b) Clinical examination.

(c) Gastric mucosal biopsy.

(d) Barium meal.

(e) Gastric photography.

(f) Gastroscopy.

(g) Estimation of maximal acid output.

(h) Haematological investigations comprising: haemoglobin; packed cell volume; mean cell haemoglobin concentration; mean cell volume; serum iron; total iron binding capacity; serum Vitamin B_{12}; parietal cell antibodies; intrinsic factor antibodies; thyroid antibodies; blood group.

(i) Faecal occult blood.

For reasons which will be discussed in the relevant chapters, it was

not possible to investigate every patient by all the parameters listed in the foregoing paragraph. The number of each investigation performed is detailed in Table III.

Investigation	Number
History and clinical examination	115
Gastric biopsy	111
Barium meal	115
Gastric photography	51
Gastroscopy	55
Maximal acid output	115
Hb., P.C.V., M.C.H.C., M.C.V.	115
Serum iron and T.I.B.C.	114
Serum Vitamin B_{12}	110
Antibodies (parietal cell, intrinsic factor, thyroid)	111
Blood group	113
Faecal occult blood	111

Table III: The number, and details, of investigations carried out.

CHAPTER 4

GASTRIC BIOPSY

Material and methods

Of the 115 patients studied, biopsy specimens of mucosa from the body of the stomach were obtained from 111. Of these, 5 were obtained at operation by opening the stomach and removing a small piece of mucosa in the course of gastric resection or pyloroplasty. In the remaining 106 patients, biopsies were obtained by the per-oral route.

Peroral biopsy was carried out using a hydraulically activated suction biopsy instrument (Quinton Instrument Co.). This instrument consists in essence of three parts (Fig. 1):

(a) the pump assembly, consisting of a carbon dioxide cylinder connected to a pressure multiplying hydraulic cylinder system controlled by an electrically operated solenoid valve. This system, in turn, has a connection with a fluid reservoir which, when in use, is filled with Tyrode's solution

(b) a double lumen tube covered with a radio-opaque metal Bowden spring, the whole being encased in a smooth polyvinyl sheath, having an external diameter of 5-6 mm. The proximal end of one of the two tubes (the 'activating' tube) is connected to a fitting on the pump assembly through which Tyrode's solution is discharged, the other 'delivery' tube being connected to a vacuum gauge to which a syringe is attached to provide suction at the distal end

(c) the biopsy capsule, 7 mm in diameter, which is connected to both 'activating' and 'delivery' components of the double lumen tube. The capsule consists of (i) the capsule proper, which is a hollow cylinder, open at one end for reception of the tube, and with a 1.5 mm side hole approximately halfway along its length (ii) a cylindrical knife, and (iii) a spring, resting on the guide pin of the knife which ensures that the knife returns to its resting position after actuation (Fig. 2).

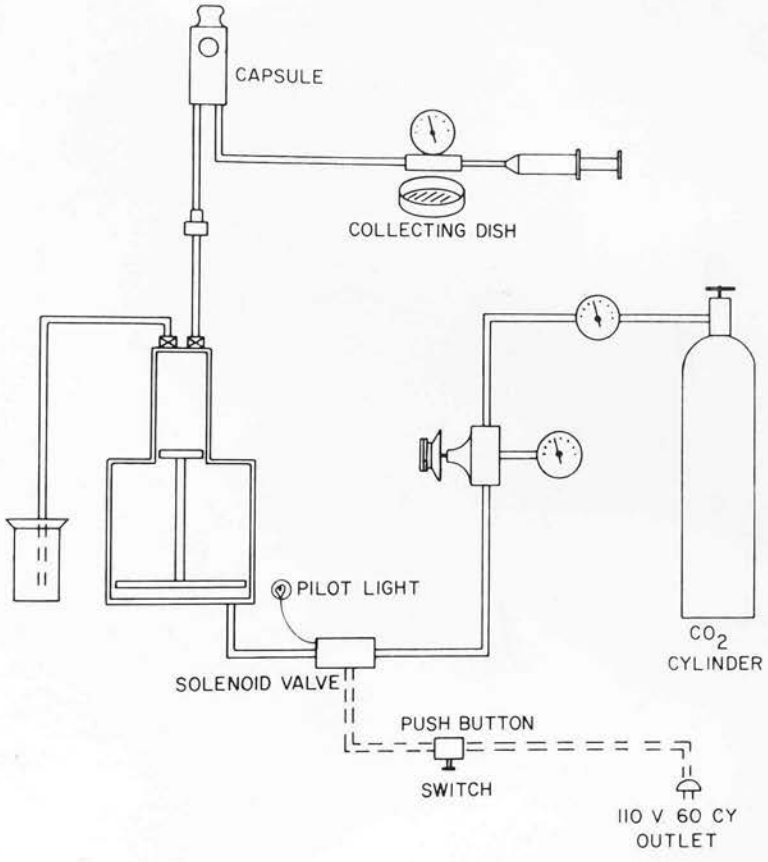


Figure 1: Hydraulic suction biopsy instrument in diagrammatic form.

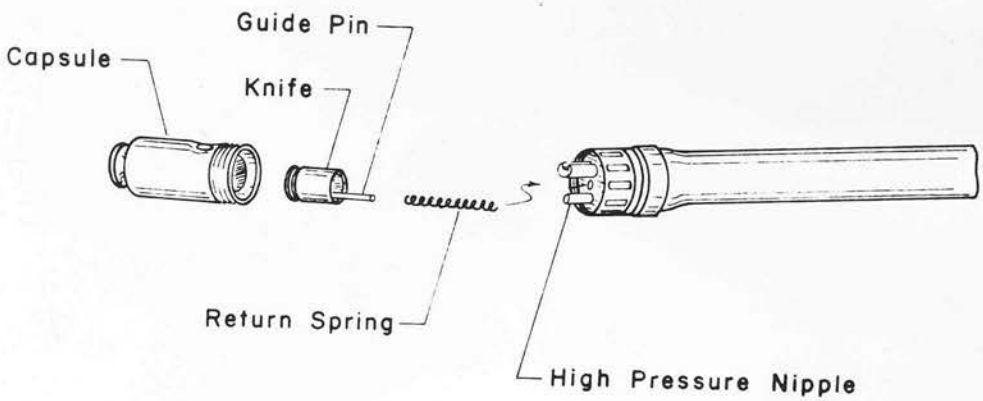


Figure 2: 'Exploded' diagram of capsule of hydraulic suction tube.

Operation Having primed the pump with Tyrode's solution, the assembly is ready for use. Suction with a syringe is applied to the vacuum gauge to a suction pressure of 5-10 inches (120-240 mm) of mercury and this is transmitted to the capsule down the delivery tube, sucking a small knuckle of mucosa into the side hole of the tube. A switch on the pump assembly is then actuated which operates the solenoid valve allowing the pump to inject approximately 50 ml of Tyrode's solution down the delivery tube at a pressure of between 60 and 80 P.S.I. This fluid, thus injected down the tube, closes the knife, opens a shunt in the capsule which allows the excised biopsy to be washed up the delivery tube. It is ejected through a side hole in the manometer which is kept closed during suction, by the operator's finger.

Though complicated in description, this beautifully engineered instrument was simple to operate, and had the merit over all other gastrointestinal biopsy instruments of having the ability not only to take multiple biopsies, but to deliver each to the operator as it was excised. It was thus never necessary to remove the tube to see whether a biopsy had been in fact taken. Failure was recognised at once, and the procedure repeated without the need for re-intubation of the patient.

Method Gastric biopsy was performed as an in-patient procedure in view of the possibility of haemorrhage resulting from its performance. Patients were starved overnight, and if there were any suggestion of pyloric obstruction, the procedure was preceded by gastric lavage with warm isotonic saline solution. Forty-five minutes prior to the procedure, 0.6 mg atropine was given subcutaneously, and half an hour and ten minutes before, the patient was instructed to suck a 10 mg berzocaine lozenge to provide surface anaesthesia. This was found to produce almost complete anaesthesia of the oro-pharynx but if atropine

was omitted, excessive salivation was often a problem. With the patient seated comfortably in a chair with the head well flexed, the tongue was held forward and the tube introduced by the mouth into the pharynx. The patient was then encouraged to swallow the tube by his own efforts, a procedure seldom accompanied by any difficulty. The tube was passed until the 55 cm mark was at the level of the incisor teeth and the patient then laid down in the left lateral position. By moving the tube up and down, and by rotating it through 90^{o} between each biopsy, an endeavour was made to obtain biopsies from anterior and posterior walls of the body of the stomach at differing levels. X-ray control was not used to localise the position of the capsule.

Multiple biopsies were taken in this way, each specimen consisting of a disc of gastric mucosa of approximately 2 mm in diameter and 0.5 mm in depth. The biopsy specimens were mounted on small pieces of No. 4 Whatman's filter paper, being gently flattened on to the paper with the side of a needle. They were then placed in 10% Formal Saline. Using this method of mounting, no specimen floated off its filter paper and it made handling of the biopsies easy at all stages in preparation. After fixation they were embedded in paraffin, and using the filter paper mount as a guide for orientation, it was a simple matter to cut the sections perpendicular to the mucosal surface, sections of 5 u thickness being cut. The sections were stained with haematoxylin and eosin, with haemaoxylin and Mayer's mucicarmine to detect alterations in mucus secreting cells, and with Motteram's trichrome staine (Motteram, 1951) for clear identification of chief and parietal cells.

Results Of the 115 patients studied, peroral gastric biopsy specimens were obtained for study in 106. In the remaining 9 patients,

the procedure failed in 8 and in 1, biopsy specimens were obtained but were lost in the laboratory. The reasons for failure were as follows: inability to swallow the tube (4); obstruction at the cardia by carcinoma (2); interference with capsule mechanism by food debris (2). Operation biopsies were obtained in 5 of these patients leaving four, all cases of gastric carcinoma, in whom no biopsy was available for study. In two further cases, biopsies of inadequate depth were obtained and the procedure was repeated successfully, and in one a biopsy of oesophageal mucosa was obtained and gastric mucosal biopsy was subsequently obtained at a second attempt (Table IV).

Multiple biopsies were taken in 92 (86%) of the 107 patients in whom the procedure was successful. Of the 15 patients in whom only a single biopsy was obtained, this was due to: failure of the capsule mechanism to cut a second biopsy (10); patient intolerance to the tube (4); bleeding (1). In the latter case, fresh blood was aspirated up the tube following the initial biopsy, and on this account it was deemed prudent to terminate the procedure. Of those in whom multiple biopsies were taken, two specimens were obtained from 23 patients, three from 50 patients, 4 from 18 patients, and 5 from 1 patient (Table V). Thus, 288 biopsy specimens were obtained by the peroral route from 107 patients of which 2 from 1 patient were lost. There were therefore 286 biopsies from 106 patients available for study, together with 5 operation biopsies from 5 further patients, making an overall total of 291 biopsy specimens from 111 of the 115 patients.

Complications Apart from the difficulties outlined above, no complications of note occurred. Minor haemorrhage occurred in one case, already mentioned, but in no other case was overt bleeding noted. No patient complained of pain, the only discomfort being

Total biopsies attempted	118
Inability to swallow tube	4
Obstruction at cardia	2
Malfunction of capsule	2
Inadequate depth of biopsy*	2
Biopsy of oesophageal mucosa*	1
Failures	11 (9.5%)
Total successful biopsies	107**

Table IV: The rate, and causes of failure, of peroral gastric biopsy using the hydraulic multiple biopsy instrument.

* successful biopsy subsequently obtained.
** less one specimen lost in laboratory.

	METHOD OF BIOPSY							
	Peroral					Operation	Total	Total studied
Number of biopsies per patient	1	2	3	4	5	1		
Number of patients	15	23	50	18	1	5	112	111
Total biopsies obtained	15	46	150	72	5	5	293	291

Table V: The number of gastric biopsies obtained by the peroral route and at operation in 112 patients from whom biopsies were obtained.

related to the passage of the tube, and this was insignificant in the vast majority of the cases.

Histology of gastric biopsies

The prepared biopsy specimens were examined by light microscopy. Study of the specimens was carried out both by the author and by a pathologist, Dr. S. W. Williams. The assessment of the histological appearances was individually carried out and the final assessment agreed where necessary after discussion and review of the sections. The categories into which gastric biopsy material is customarily assigned are four, namely:- normal mucosa; superficial gastritis; atrophic gastritis; gastric atrophy (Doig, 1949; Doig and Motteram, 1949-50; Motteram, 1951; Doig and Wood, 1952; Joske, Finckh and Wood, 1955; Wood and Taft, 1958).

Normal mucosa

Normal mucosa from the body of the stomach (Fig. 3) consists of a dense aggregation of branched tubular glands opening into the foveolae gastricae or gastric pits. Parietal cells are numerous especially in the superficial portion of the glands and are polyhydral in shape with an eosinophilic cytoplasm. The pepsin secreting chief cells are found mostly in the deeper portions of the glands, and are cuboidal or low columnar in shape with basal nuclei and a granular cytoplasm. The superficial epithelium of the mucosa consists of a regular single layer of tall columnar epithelium with a pale eosinophilic cytoplasm containing mucigenic granules and a basal nucleus. The surface epithelium extends into the pits which extend down into the mucosa for a distance of from one-third to one-half of its depth. The lamina propria lies as a thin layer between surface epithelium and glands for which latter structures it forms a thin basement membrane. Immediately deep to the glands lies the muscularis mucosae.

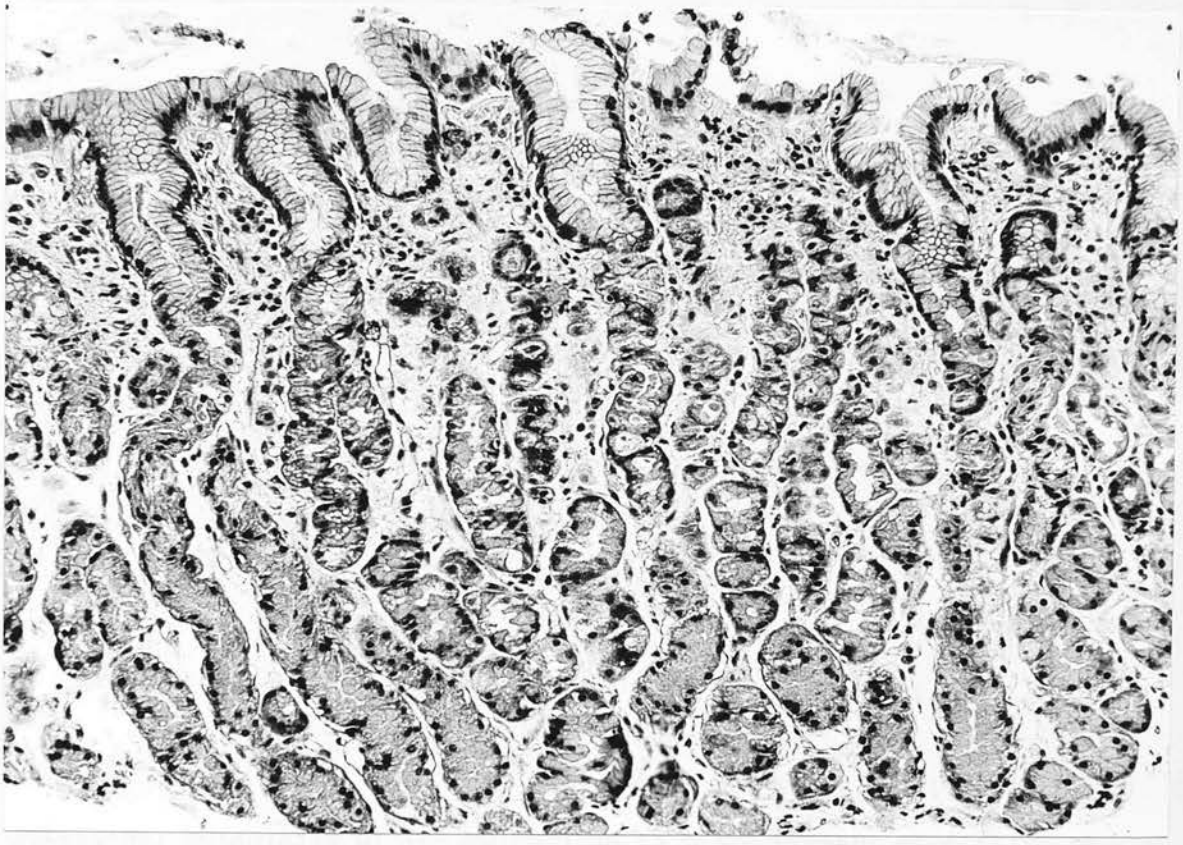


Figure 3: Normal gastric body mucosa x 200 stained haematoxylin and eosin.

In the pyloric antrum and cardia, the gastric pits are deeper and the glands consist of coiled tubules lined by low columnar or cuboidal epithelium with a greater amount of interglandular cellularity than is found in body mucosa (Maximow and Bloom, 1952; Wood and Taft, 1958).

Superficial gastritis (Fig. 4)

In this condition there is superficial inflammation of the mucosa without glandular atrophy. The inflammatory infiltrate consists of plasma cells and polymorphonuclear leucocytes in differing proportions and is confined to the subepithelial layer of the lamina propria. It does not extend into the glandular portion of the mucosa, the glands containing a normal number of parietal and chief cells. The thickness of the mucosa does not differ from normal.

Atrophic gastritis (Fig. 5)

Atrophic gastritis differs from the above in that (a) the inflammatory infiltrate extends down to the muscularis mucosae between the glands, and (b) there is atrophy of the glands themselves. The glands are reduced in number and the number of parietal and chief cells are fewer and many do not stain for acid or pepsin with trichrome stain. The surface epithelium is often flattened and the nuclei hyperchromatic, more than one layer of surface epithelial cells being often seen. Intestinal metaplasia of the epithelium is often present especially in the more severe forms where patches of goblet cells are seen replacing the normal surface epithelium, and extending into the gastric pits in whose bases Paneth cells are not infrequently found (Fig. 6). The muscularis mucosae is often fragmented, and strands of muscle are seen in the inflammatory infiltrate between atrophic glands. In severe forms of atrophic gastritis the depth of the mucosa is reduced but in less severe grades the inflammatory infiltrate is such that it fills

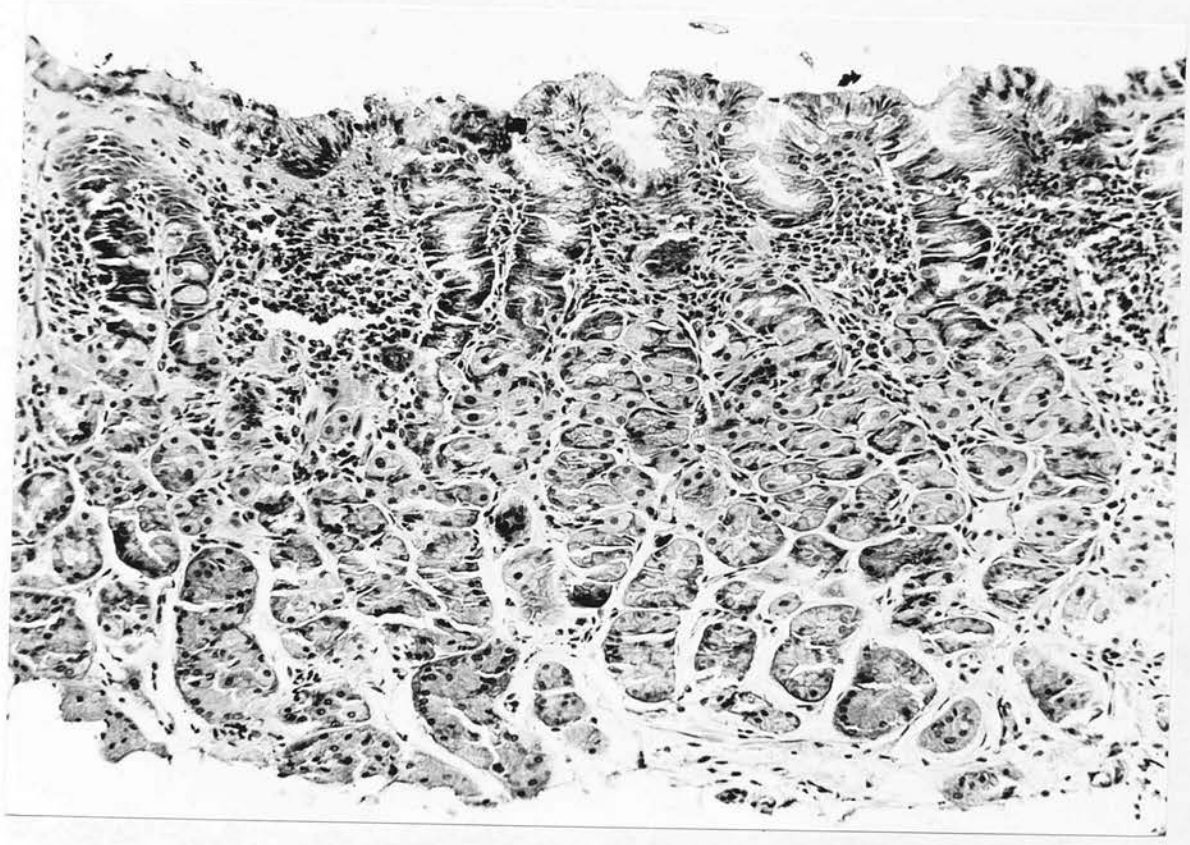


Figure 4: Superficial gastritis x 200 stained haematoxylin and eosin.

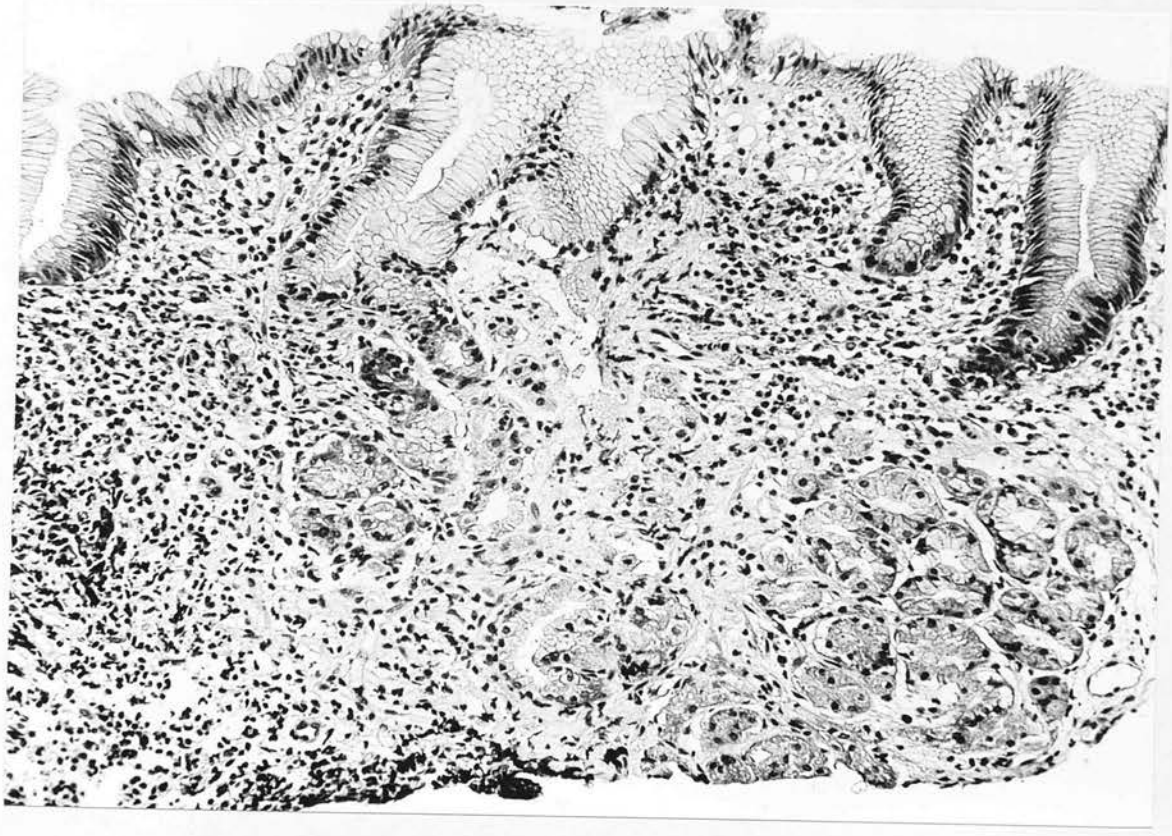


Figure 5: Atrophic gastritis x 200 stained haematoxylin and eosin.

Figure 6: Severe atrophic gastritis with intestinal metaplasia x 200 stained haematoxylin and eosin.

the space left by the atrophying glands with no significant reduction in the overall mucosal thickness.

Gastric atrophy

Gastric atrophy (Fig. 7) is customarily described as a separate entity though the differentiation between it and severe atrophic gastritis is indistinct. There is complete atrophy of the glands and little or no inflammatory infiltrate in a thin mucosa whose surface is often thrown into a villous pattern with extensive intestinal metaplasia.

The histological changes described above form a continuous spectrum ranging from normality to gastric atrophy and the dividing line between one group and another is indistinct and is subject to variations of interpretation. Minor degrees of chronic inflammation in the stroma and irregularities of the surface epithelium are not infrequently found in mucosa whose glandular pattern is otherwise normal. The differentiation between this and superficial gastritis is not clear, when glandular atrophy is absent or slight. Joske and his co-workers (1955) in a study of 1000 biopsies sub-divided their biopsy findings into seven categories, namely:- normal, slight superficial gastritis, moderate or severe superficial gastritis, superficial gastritis with atrophy, atrophic gastritis, severe atrophic gastritis, and gastric atrophy. Such an elaborate morphological classification in a large series is of value and histological interest, but it was felt that to employ such a classification in a clinical study would lead to confusion rather than clarity.

In this study the presence or absence of glandular atrophy was employed as the index against which other parameters were compared. Judged by the number of parietal cells and the degree of atrophy of the glands, a score was given from 1, where atrophy was slight, to 6, where atrophy was complete. The degree of inflammatory infiltration of the

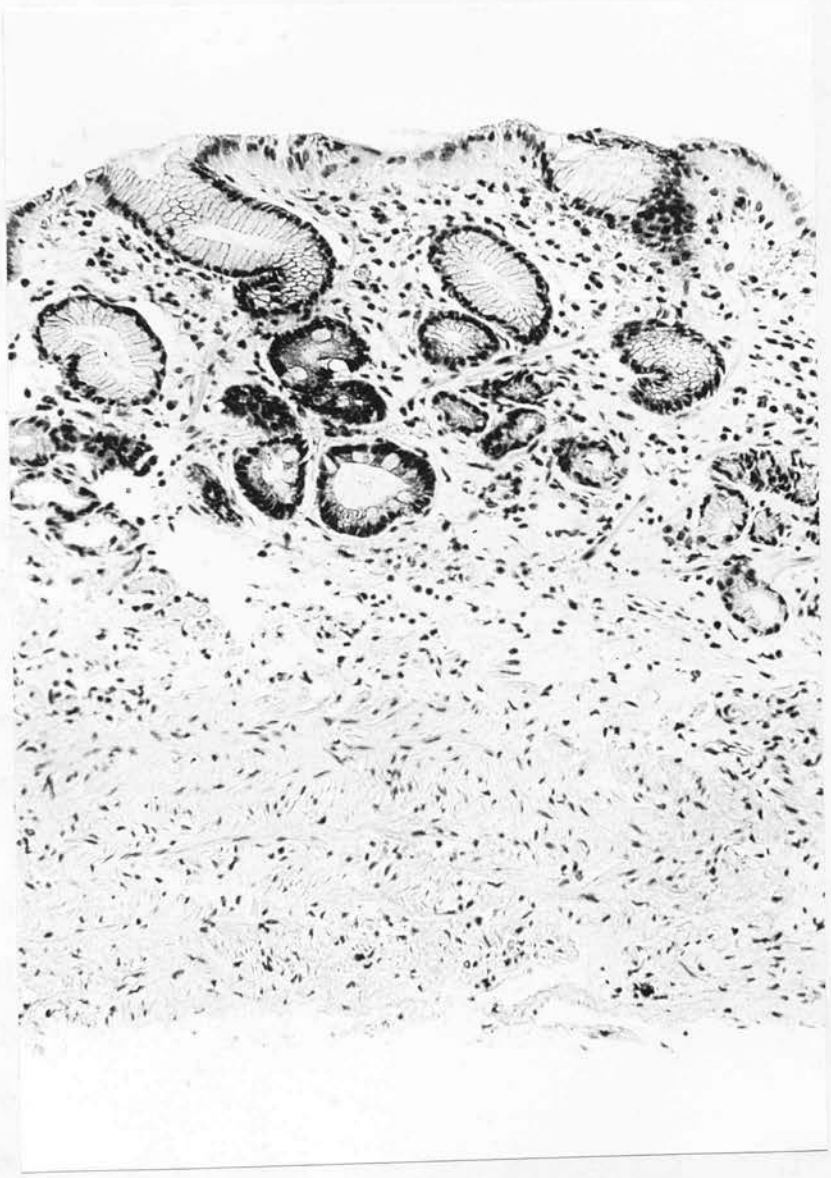


Figure 7: Gastric atrophy showing islands of intestinal metaplasia x 200 stained haematoxylin and eosin.

stroma was variable. The differing grades of atrophic gastritis have been grouped according to the classification in Table VI. Those cases with superficial gastritis, as defined above, and without atrophy, and those cases with minor miscellaneous inflammatory changes, have been grouped together under the heading of 'superficial gastritis'. They are discussed separately in certain sections of the text, but generally are included in the 'non-atrophic' group. In those cases with glandular atrophy, inflammation was usually present throughout the whole depth of the stroma. In those with principally superficial inflammation accompanied by some degree of atrophy, however, they have been included in the 'atrophic' group, though they might correspond to 'superficial gastritis with atrophy' in Joske's classification. The presence or absence of intestinal metaplasia was recorded. Justification for this method of classification will be advanced when the biopsy findings are discussed and correlated with other results.

Multiple biopsies of gastric body mucosa were available for study from 91 patients. As an estimate of the sampling error inherent in blind gastric biopsy, the appearances of these multiple biopsies were compared. They were similar in 83 (91.2%) of the cases. In the remaining 8 cases they were dissimilar, and the most abnormal biopsy from these patients has been used in their assessment.

The assessment of the histological appearances and allocation of patients into categories according to the gastric biopsy findings was carried out separately by the author and by a pathologist. After an initial examination by the author and assessment of the degree of glandular atrophy present, the sections were re-examined

by him without reference to the original findings. The results of these two studies were then compared. No difference in the assessment of those graded 0 nor of those graded 5-6 was found between these two assessments. Of the 41 subjects in whom a grade of atrophy from 1-4 had been given, the assessment in 7 (17%) differed on the two occasions. The different assessments given, however, all fell within grades 1-4. These sections were re-examined and a final assessment given. The results of the author's and of the pathologist's assessment were then compared and again no disagreement was found between those designated as having non-atrophic mucosa (grade 0) and those with severe (grade 5-6) atrophic changes. When the remainder were grouped into 'mild' or 'moderate' atrophic gastritis (grade 1-2 or 3-4 respectively), disagreement was found in 4 instances (10%), all, however, being graded between grade 1 and grade 4 by both observers. The sections from these patients were then re-examined jointly and a final agreed assessment given.

FINDINGS

The overall gastric biopsy findings in the patients studied are summarised in Table VII. Normal mucosa was found in 28 and superficial gastritis in 12, providing a total without evidence of glandular atrophy of 40 or 36% of the total examined. Of the remaining 71 cases (64%) with evidence of atrophy, 15 had 'mild' atrophic gastritis, 26 'moderate' and 26 'severe' changes. Gastric atrophy without inflammation was found in 4 cases, all with pernicious anaemia.

Histological appearances	Number		
Normal mucosa	28	Non atrophic	40
Superficial gastritis	12		
Atrophic gastritis Grade 1	8	Mild atrophic gastritis	15
Atrophic gastritis Grade 2	7		
Atrophic gastritis Grade 3	10	Moderate atrophic gastritis	26
Atrophic gastritis Grade 4	16		
Atrophic gastritis Grade 5	17	Severe atrophic gastritis	26
Atrophic gastritis Grade 6	9		
Gastric atrophy	4		
Total	111		
No biopsy available	4		
Total	115		

Table VI: The histological findings on gastric biopsy of 111 dyspeptic patients over the age of 40 years.

Diagnosis	Total	MUCOSAL HISTOLOGY						
		Normal	Superficial gastritis	Atrophic gastritis Mild	Mod.	Severe	Gastric atrophy	Total atrophic
Duodenal ulcer	22	13	4	3	1	1		5 (23%)
Gastric ulcer	21	3	3	5	6	4		15 (71%)
Gastric carcinoma	19*	1	1	3	11	3		17 (90%)
Non-ulcer dyspepsia	40	11	4	4	6	15		25 (63%)
Pernicious anaemia	9				2	3	4	9 (100%)
Total	111	28	12	15	26	26	8	71 (64%)

Table VII: The distribution of gastric mucosal findings in 111 dyspeptic patients according to diagnosis.

*excluding four cases in whom histology was not available.

Diagnosis

When the mucosal histology was studied in relation to clinical diagnosis (Table VII), atrophic gastritis or gastric atrophy was found as expected in all cases of pernicious anaemia. Its highest incidence otherwise was amongst the 19 cases of gastric carcinoma, of whom 17 had atrophic gastritis, moderate or severe in all but 3, an overall incidence of 90%. The lowest incidence was in the duodenal ulcer group where atrophic gastritis was found in 5 cases (23%) of whom 1 was of moderate grade, and 1 severe. The gastric ulcer and non-ulcer dyspepsia group occupied an intermediate position with 15 (71%) and 25 (63%) respectively, the latter group having a preponderance of severe grades.

Age

When compared with the age of the patients studied, it will be seen from Table VIII that the incidence of atrophic gastritis rose from 54% of 24 patients between 40 and 50 years of age, to 72% of the 29 patients of between 60 and 70, and 71% of those over 70. The proportion of the three grades of atrophic gastritis was different in each group but from a study of Figure 8 it will be seen that there was no striking increase in the proportion of cases of severe atrophic gastritis with increasing age. Excluding 9 cases of pernicious anaemia the incidence of atrophic gastritis was 54% from 40-49, 53% from 50-59, 59% from 60-69 and 66% from 70-80 years. These differences are not significant ($x^2 = 1.95$ $df = 3$ $p > 0.5$).

Sex

Seventy-three male and 38 female patients were studied, with a mean age for males of 58.4 and for females 63.6 years. Of the males, 41 (56%) had atrophic gastric mucosa compared with 30 (82%) of the females (Table IX). If the 9 cases of pernicious anaemia, 6 male and 3 females,

Age	No.	GASTRIC MUCOSAL APPEARANCES						Total Atrophic
		Normal	Superficial gastritis	Atrophic gastritis Mild	Mod.	Severe	Gastric atrophy	
40-50	24	7	4	3	6	4	1	13 (54%)
51-60	30	9	4	4	6	7	1	17 (57%)
61-70	29	7	1	3	7	8	3	21 (72%)
70-80	28	5	3	5	7	7	1	20 (71%)
Total	111	28	12	15	26	26	6	71 (64%)

Table VIII: The distribution of gastric mucosal findings in 111 dyspeptic patients according to age.

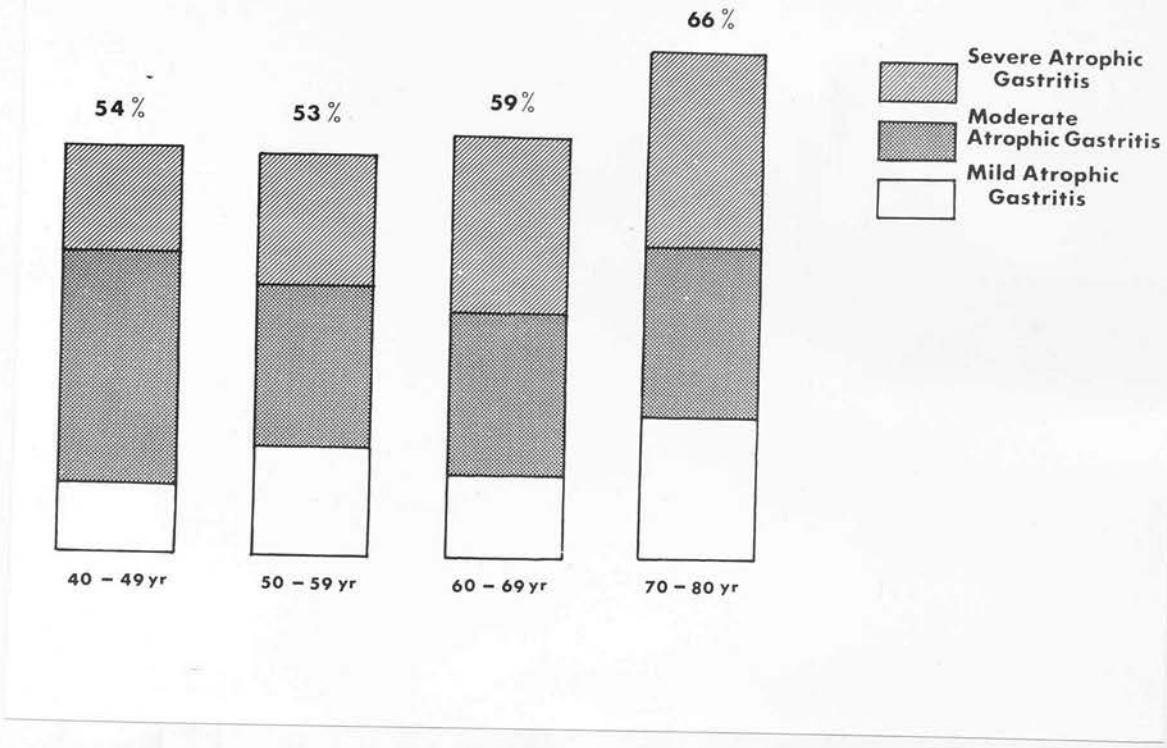


Figure 8: The incidence of atrophic gastritis according to age showing the proportion of each grade of severity in each decade. The histograms are expressed as percentages of the total number of subjects in each age group, excluding all cases of pernicious anaemia.

Sex	No.	GASTRIC MUCOSAL APPEARANCES						
		Normal	Superficial gastritis	Atrophic gastritis Mild	Mod.	Severe	Gastric atrophy	Total Atrophic
Male	73	22	10	9	16	14	2	41 (56%)
Female	38	6	2	6	10	12	2	30 (82%)

Table IX: The distribution of gastric mucosal changes related to sex in 111 subjects.

are excluded from these figures, the incidence of atrophic gastritis in males of 50% compares with an incidence of 77% in females. This difference is statistically significant ($x^2 = 5.91$ d.f. = 1 $p < 0.02$).

Intestinal metaplasia

Intestinal metaplasia was not found in the biopsy of any of the 40 cases with non-atrophic mucosa, and was found in 42 (59%) of those with atrophic changes, the overall incidence in the 111 cases studied being 38%. As will be seen from Table X the incidence in those with mild atrophic gastritis was 44%, 57% in those with moderate changes, 61% with severe atrophic gastritis and 75% with gastric atrophy. The incidence therefore rose with increasing severity of atrophic change but this rise was not statistically significant ($x^2 = 1.13$ d.f. = 3 $p > 0.7$).

The incidence of intestinal metaplasia was compared with the clinical diagnosis of the patients. This change was not found in any patient with duodenal ulcer, was found in 37% of those with non-ulcer dyspepsia, 48% of those with gastric ulcer, 53% of those with carcinoma and 77% of the pernicious anaemia patients (Table XI).

The incidence of intestinal metaplasia was compared with the sex and age of the patients. Comparing those of each sex with atrophic mucosa, no significant difference was found in its incidence between the sexes, it being found in the mucosa of 56% of males and 63% of females ($x^2 = 0.39$ d.f. = 1 $p > 0.5$) (Table XII). The incidence occurring in each decade studied rose from 38% between 40 and 50 to 75% in those over the age of 70 (Table XIII). No significant difference was found in the incidence between the 40 - 49 and 50 - 59 decades or between the 60 - 69 and the over-70 decades but a highly significant difference was found between the incidence of intestinal metaplasia in those under and those over the age of 60 years ($x^2 = 7.6$ d.f. = 1 $p < 0.001$).

	Total no.	Intestinal metaplasia no.	Incidence %
Normal	28	0	0
Superficial gastritis	12	0	0
Atrophic gastritis			
Mild	15	7	44
Moderate	26	15	57
Severe	26	17	61
Gastric atrophy	4	3	75
	111	42	38

Table X: The incidence of intestinal metaplasia compared with the gastric mucosal findings in 111 cases.

	Total	Not atrophic	Atrophic	Intestinal metaplasia		
				No.	% of total	% of atrophic
D.U.	22	17	5	0	0	0
N.U.D.	40	15	25	15	37	6
G.U.	21	6	15	10	48	66
Ca.	19	2	17	10	53	59
P.A.	9	0	9	7	77	77
	111	40	71	42	38	59

Table XI: The incidence of intestinal metaplasia related to clinical diagnosis and to the presence or absence of atrophic gastric mucosal changes.

	Total	Total atrophic	Intestinal metaplasia		
			No.	% of total	% of atrophic
Male	73	41	23	32	56
Female	38	30	19	50	63
Total	111	71	42	38	59

Table XII: The incidence of intestinal metaplasia related to the sex of the patients studied.

	Total	Total atrophic	Intestinal metaplasia		
			No.	% of total	% of atrophic
40 - 50	24	13	5	21	38
51 - 60	30	17	7	23	41
61 - 70	29	21	15	52	71
71 - 80	28	20	15	54	75
Total	111	71	42	38	59

Table XIII: The incidence of intestinal metaplasia related to the age, by decades, of the patients studied.

DISCUSSION

Method

The hydraulic biopsy instrument was found to be a safe and simple method of obtaining multiple biopsies of gastric mucosa. No serious complications resulted from its use in the 118 instances when it was employed. Although the tube was a little larger than the more conventional biopsy tubes (Wood, Doig, Motteram and Hughes, 1949; Coghill and Williams, 1955) it was passed easily and without significant patient discomfort on 112 (95%) of 118 occasions. Using a modified Wood tube, Joske and his co-workers (1955) reported an incidence of haemorrhage following biopsy in 0.8% of 1226 cases, and Siurala, Isokoski, Varis and Kekki (1968) using a Sielaff biopsy tube had an incidence of 1.4% in 142 biopsies. Christiansen and Johansen, using a Crosby capsule (Crosby and Kugler, 1957) reported haemorrhage following gastric biopsy in 3% of 98 cases. The failure rate of 5% in the group of patients being reported compares with 15% reported in Joske's series, in which 39% of his first 100 biopsies failed, Siurala had a failure rate of 3% and Christiansen and Johansen 2%. Inadequate specimens (2 too thin and 1 oesophageal mucosa) were obtained in 3 cases (2.5%), compared with 10% in Joske's series and 7% in Christiansen's. Ninety-one per cent of multiple biopsies taken from individual patients showed similar appearances. In Joske's series of 726 cases in which 2 pieces of mucosa were taken from different parts of the body of the stomach, similar appearances were found in 73.8% and in Siurala's series 89% of multiple biopsies showed similar histological patterns. Of 200 cases, Wynn Williams, Edwards, Lewis and Coghill (1957) found notable differences in histology between biopsies in the same patient in 6.5%, and in 342 cases Henning (1968) found differences in 12%. In none of these studies was the combination of normal mucosa and atrophic gastritis found, the differences

being either between normal mucosa and superficial gastritis, or between degrees of gastritis with atrophy. From the findings in the present study and the experience of others, it therefore seems clear that a single gastric biopsy is likely to be representative of the general state of the gastric body mucosa, and that the changes found are diffuse in at least the considerable majority of cases.

The incidence of atrophic gastritis in the population is not known, and the only random population study which has been reported comes from a small village population in Finland (Siurala et al., 1968), already discussed. Other published series relate either to selected age groups (Palmer, 1954; Russell, Aziz, Ahmad and Kent, 1966; Andrews, Haneman, Arnold, Cooper Booth and Taylor, 1967) or to selected groups of hospital subjects (Motteram, 1951; Palmer, 1952; Joske, Finckh and Wood, 1955; Wynn Williams, Edwards, Lewis and Coghill, 1957). The incidence of the finding of atrophic and non-atrophic mucosa in these series is summarised in Table XIV which relates to published series irrespective of age, and Table XV in which the incidence in patients over the age of 40 has been extrapolated for comparison with the present study. It will be seen that a wide variation in the incidence of atrophic gastritis exists in the various studies and, to a certain extent, this is dependent upon the interpretation of the lesser changes which are found. Joske and his co-workers sub-divide 'superficial gastritis' into 3 grades, two without and one with atrophy. Motteram (1951) refers to 'superficial gastritis with minimal atrophy' in 33% of his cases, but Wynn Williams et al state that most of these cases would fall into their category of 'miscellaneous minor lesions', while some of the cases of 'superficial gastritis' would have been designated by them as 'chronic atrophic gastritis'. Wynn Williams defines superficial gastritis as exhibiting atrophy of the superficial glands, while Siurala and his co-workers (1956, 1966 and 1968),

	No. studied	Not atrophic	Atrophic	Comment
Motteram, 1951	150	37%	63%	Dyspeptic Ages not stated
Palmer, 1952	105	100%	Nil	No G.I. symptoms Aged 18 - 67
Joske et al., 1955	1000	60%	40%	66% with G.I. symptoms Ages not stated
Wynn Williams et al., 1957	200	66%	33%	Non-ulcer dyspepsia Aged 18 - 73
Siurala et al., 1968	142	72%	28%	Aged 18 - 73

Table XIV: The incidence of atrophic gastritis in previously published studies of subjects irrespective of age.

	No. studied	Not atrophic	Atrophic	Comment
Palmer, 1954	30	100%		Over 60 years of age No digestive symptoms
Joske et al., 1955	336	56%	44%	Over age 40 Many with dyspepsia
Wynn Williams et al., 1957	79	65%	35%	Over age 40 N.U.D.
Andrews et al., 1967	24	4%	96%	Over age 64 No digestive symptoms
Siurala et al., 1968	70	56%	44%	Over age 40 Random study
Present study	102	39%	61%	Over age 40 All dyspeptic (excludes cases of P.A.)

Table XV: The incidence of atrophic gastritis in previously published studies of subjects over the age of 40, compared with the present study.

Wood and Taft (1958) and others define superficial gastritis as it has been defined in this study, and as exhibiting no atrophy of the glandular epithelium. Wynn Williams and his colleagues differentiate between 'minor mucosal lesions' and 'superficial gastritis'. In the former, the glandular pattern is normal, but the surface epithelium or the stroma or both are abnormal, with irregularities in the size, shape and numbers and staining properties of surface cells and a mild excess of chronic inflammatory cells in the stroma. In the latter, there is atrophy of the glands in the superficial part of the mucosa with a chronic inflammatory infiltrate in this region.

There is much less room for confusion in the interpretation of biopsies in which the mucosa shows more severe atrophic gastritis or gastric atrophy. If those with 'mild atrophic gastritis' are excluded, the incidence of moderate and severe atrophic gastritis in our patients, excluding those cases with pernicious anaemia, is 52%, compared with an incidence of 'atrophic gastritis' of 33% (Motteram, 1951), 23% (Joske, 1955), 33% (Wynn Williams, 1957) and 44% (Siurala, 1968), the latter two relating to patients over the age of 40 years.

Clinical diagnosis

Five (23%) of the 22 cases of duodenal ulcer had evidence of atrophic gastritis, this being mild in 3, moderate in 1 and severe in 1 case. Superficial gastritis was found in 4 (18%), the remaining 13 cases being normal mucosa. The one case with severe atrophic gastritis was a woman of 77 years with long-standing duodenal ulceration and a maximal acid output of 3.1 mEq/hour. The case with moderate atrophic gastritis was a male of 47 years with chronic duodenal ulceration, an acid output of 37.8 mEq/hour. It is difficult to explain this finding except on the grounds of the chance occurrence of biopsying a small area of patchy gastritis. Two biopsies were, however, taken from this

case. These findings compare with normal mucosa being found in Joske's series in 60% of duodenal ulcer patients, superficial gastritis in 30%, i.e. 90% showing no evidence of atrophy, compared with 77% in the present series. His incidence of atrophic gastritis of 10% compares with 23% in our series, or if only those with moderate and severe changes are taken into consideration, 9%. The finding of atrophic gastritis in cases of duodenal ulceration is difficult to reconcile with the nature of the condition, and the finding of a high acid output lends support to the view expressed by Shiner and Doniach (1957) that while usually the case, gastric biopsy does not invariably reflect the general state of the gastric mucosa. This paradox will be further discussed in relation to the acid secretory studies in this group.

A high incidence of atrophic gastritis was found among the gastric ulcer patients of whom only 6 (29%) had non-atrophic mucosa. Ten (48%) had moderate or severe changes while the remaining 5 had mild atrophic gastritis. These findings compared with an incidence of atrophic change in 45% of Joske's group of 65 gastric ulcer patients and are in accord with the findings of Magnus (1952) who found a high incidence of atrophic gastritis in a study of resected specimens for gastric ulcer, and Ringertz (1961) who reports an incidence of atrophic gastritis in the body of the stomach in 60% of cases of benign gastric ulcer.

Of the 19 cases of gastric cancer studied by mucosal biopsy, all but 2 had evidence of atrophic gastritis and the changes were moderate or severe in 14, 74% of the total. These findings compare with an incidence of atrophic gastritis in association with gastric cancer of 97% (Guiss and Stewart, 1943), 50% (Joske, Finckh and Wood, 1955), 80% (Ringertz, 1961) and 53.3% (Valencia-Parpacen and Romer, 1965).

The gastric mucosa of the 40 cases with non-ulcer dyspepsia is of interest. Not only may any mucosal abnormalities be looked upon as

a condition per se in these cases, rather than as a possible sequel to, or factor associated with, ulceration or malignant disease, but the group fortuitously consisted of equal numbers of males and females with a mean age of 57.5 years, and 62.4 years respectively. Though dyspeptic and a small group, they may give at least some indication of the incidence of gastric mucosal abnormalities in the population from which they derive. Of the 40 studied, 11 had mucosa within normal limites, 4 superficial gastritis, and 25 atrophic gastritis which was mild in 4, moderate in 6 and severe in 15. Atrophic change was present in 10 (65%) of the males and in 15 (75%) of the females (Table XVI). While these figures indicate a higher incidence in females this difference did not reach statistical significance ($x^2 = 2.66$ d.f. = 1 $p > 0.1$).

The incidence and severity of atrophic change, when compared with age, showed a higher overall incidence with age but no increase in the proportion of severe grades of the condition with advancing years (Table XVII). The increased incidence with age did not reach statistical significance ($x^2 = 0.56$ $p > 0.3$). While it appears that atrophic gastritis is commoner in older than in younger people, a significant difference was not found either in the group as a whole or in the non-ulcer dyspeptic group. The highly significant difference between the sex incidence in the group as a whole was not reflected in the non-ulcer dyspeptic group and it may be inferred that this was due to bias introduced by the preponderance of male patients with duodenal ulcer in the overall male group.

The incidence of atrophic gastritis in non-ulcer dyspepsia has been investigated by Shiner and Doniach (1956), Wynn Williams and his colleagues (1957), and by Motteram (1951) whose findings are compared with the present group in Table XVIII. Motteram found 33% of his cases had moderate to severe atrophic gastritis, compared with 52.5% in this

	Total	Normal mucosa	Superficial gastritis	Atrophic gastritis			Total no.	Atrophic %
				Mild	Mod.	Severe		
Male	20	7	3	2	2	6	10	65
Female	20	4	1	2	4	9	15	75
Total	40	11	4	4	6	15	25	62.5

Table XVI: The gastric mucosal biopsy findings in 40 cases of non-ulcer dyspepsia, related to sex.

Age	Total	Normal mucosa	Superficial gastritis	Atrophic gastritis			Total no.	Atrophic %
				Mild	Mod.	Severe		
40 - 50	9	2	2	0	2	3	5	55
51 - 60	12	4	1	1	3	3	7	58
61 - 70	7	2	0	1	0	4	5	71
71 - 80	12	3	1	2	1	5	8	66
Total	40	11	4	4	6	15	25	62.5

Table XVII: The gastric mucosal biopsy findings in 40 cases of non-ulcer dyspepsia, related to age.

	No.	Normal mucosa	Superficial gastritis	Atrophic gastritis
Motteram (1951)	150	37%	30%	33%
Shiner and Doniach (1956)	50	66%	16%	18%
Wynn Williams et al (1957)	124	42%	39%	23%
Present study	40	28%	10%	62%

Table XVIII: The gastric biopsy findings in non-ulcer dyspepsia in the present study compared with previously published studies.

study, and, in addition, a further 30% he defined as 'superficial gastritis with minimal atrophy'. Wynn Williams and his group found 23% with atrophic gastritis and a further 6% with superficial gastritis, defined as showing atrophy of the glands in their superficial part and infiltration of the stroma in this region with numerous inflammatory cells. In addition, a further 33% had minor mucosal abnormalities but without atrophy. In Shiner and Doniach's series, 18% had atrophic gastritis, 16% 'gastritis without gross atrophy', the remainder having normal mucosa. The mean age of this group was approximately 45 years.

These comparisons serve to underline the difficulties of interpretation of gastric biopsies especially in the presence of lesser changes, and stress the need for careful matching of age and sex in addition when comparisons of incidence are made. Until there is agreement upon nomenclature, the validity of such comparisons between population groups is of little value, and any conclusions drawn from them concerning the influences of genetic or environmental factors in the incidence of atrophic gastritis can have little meaning.

Intestinal metaplasia

The finding of intestinal metaplasia in all grades of atrophic gastritis stresses the importance of differentiating between atrophic and non-atrophic mucosa in which it was not found. The incidence of this feature in 59% of all cases with atrophic gastritis compares with 42% in the random study of Siurala and his colleagues, but its incidence has not been stressed in other biopsy series. Morson (1955) from a study of operation and autopsy specimens found that its incidence was higher in the pyloric antrum than in the body of the stomach, irrespective of the morbid condition for which the stomach was being examined. The incidence in body mucosa was 9.6% in cases with duodenal ulcer, 39.3% in cases with

gastric ulcer, and 66.7% in the presence of gastric cancer and the severity and extensiveness of the change followed a similar pattern. Both he and Siurala found no difference in its incidence between the sexes, but, being a feature of atrophic gastritis, the incidence of intestinal metaplasia increased with advancing age. While intestinal metaplasia was not found in patients with otherwise normal gastric body mucosa in the study, it was also not found associated with the atrophic gastritis present in five duodenal ulcer cases in the present series. The incidence in duodenal ulcer in Morson's series was low, and Magnus (1937) found it to be present in 20% of stomachs resected for duodenal ulcer compared with 60% of stomachs with malignant ulcer and 74% with benign ulcer.

It may be said, therefore, that intestinal metaplasia is a feature of atrophic gastritis, it is commoner in severe forms of this condition but may occur in association with quite minor changes. It is least common in duodenal ulceration, a condition carrying a low risk of gastric cancer, but is common in the presence of both benign and malignant gastric ulcer, to which latter condition it appears to bear an aetiological relationship. It is a common finding, and its detection as a possible pre-cancerous condition rests upon the detection of atrophic gastritis.

CHAPTER 5

CLINICAL ASPECTS

The clinical history of each patient was taken by the author with particular reference to (a) the presenting symptoms (b) the family history, and (c) the social history.

Symptomatology All patients had dyspeptic symptoms and in many it was difficult to obtain a clear-cut description of their subjective complaints. With a view to analysis, the symptoms complained of were divided into three groups, namely:- (a) pain, which ranged from discomfort to severe pain (b) nausea, which ranged from anorexia and epigastric fullness to an actual desire to vomit, and (c) vomiting. The duration of symptoms was investigated and again, as is familiar, it was difficult to ascertain with any exactitude how long the symptoms had been present in many individuals. For purposes of analysis the duration of symptoms was broken down into five sub-groups, namely:- (a) less than one year (b) one to five (c) five to ten (d) ten to twenty, and (e) over twenty years.

In addition to the symptoms of dyspepsia, a history of haematemesis or melaena was specifically sought as was a history of weight change. This was a symptom again difficult to evaluate on account of its being frequently a subjective impression, with no measurable or objective parameters.

Family history A family history was taken relating to parents, grandparents and siblings. Following a general inquiry as to the family history, specific enquiry was made as to the existence in the family of a history of gastric disorder, cancer, pernicious anaemia and goitre. Patients varied in their ability to recall details, and only specific occurrences of these conditions were recorded, 'stomach trouble', 'indigestion' and such vague descriptions were discounted.

Social history The place of origin of each patient was noted as was his or her occupation and social class (all the patients living in either a

working class or middle class environment). An attempt was made to record their dietary habits but this did not prove a fruitful line of enquiry, except that none was vegetarian.

Smoking and dietary habits were investigated and, for the purposes of analysis, were broken down into three sub-groups. With regard to smoking, these consist of (a) non-smokers or those smoking only infrequently (b) those consuming between 10 and 20 cigarettes (or pipe tobacco equivalent) per day, and (c) those smoking 20 or more cigarettes or equivalent daily. It was more difficult to group the subjects into a simple classification according to alcohol intake. The classification shown in Table XIX consists of three groups: (a) those never taking alcohol and occasional drinkers (b) moderate drinkers who took less than 2 pints of beer (or equivalent) per day, and (c) regular drinkers taking in excess of 2 pints of beer or equivalent per day. No alcoholics were included in this study as far as could be ascertained. It is common experience that patients tend to minimise their consumption both of tobacco and alcohol when giving a medical history, and any analysis of this type of data is subject to limitations on this account.

Clinical examination A clinical examination of each patient was carried out, special note being taken of any abnormalities in the abdomen, notably tenderness, organ enlargement or the presence of a palpable mass.

RESULTS

History (Table XIX)

Pain This was the most frequent complaint, being recorded in 95 of the 115 patients studied. Of the 43 peptic ulcer patients, all but two complained of pain, and this symptom was a feature in 74% of gastric cancer patients and 83% of those with non-ulcer dyspepsia. It was thus a symptom of little value in differentiating between the groups, though its periodicity and relationship to meals was more distinct in the ulcer patients.

Diagnosis	No.	Presenting symptoms			
		Nausea	Vomiting	Pain	Weight loss
Duodenal ulcer	22	10 (45%)	12 (55%)	22 (100%)	9 (41%)
Gastric ulcer	21	12 (57%)	5 (24%)	19 (90%)	9 (33%)
Gastric cancer	23	17 (74%)	11 (48%)	17 (74%)	20 (87%)
Non-ulcer dyspepsia	40	32 (80%)	17 (43%)	33 (83%)	25 (63%)
Pernicious anaemia	9	8 (88%)	1 (11%)	4 (44%)	4 (44%)

Table XIX: The presenting symptoms complained of by the patients studied.

Nausea This symptom was more commonly associated with those with cancer and non-ulcer dyspepsia than with those with peptic ulceration, but vomiting though least common in the gastric ulcer patients and those with P.A., was fairly evenly distributed throughout the rest of the group, being recorded in approximately half the patients with duodenal ulcer, cancer and non-ulcer dyspepsia. Weight loss was recorded in the history of 67 of the patients (60%), weight gain only being recorded in 2. It was commonest in those with cancer, but was noted in the history of 63% of those with non-ulcer dyspepsia, 44% with P.A., 41% with duodenal ulcer and 33% with gastric ulcer.

The length of history of dyspeptic symptoms was studied in relation to diagnosis and to gastric histology. It was of some help in differentiating between those with duodenal ulcer and the remaining group. Only 14% of duodenal ulcer patients had a history of less than a year, compared with 65% of cancer patients and 40 and 48 per cent of those with non-ulcer dyspepsia and gastric ulcer respectively. A history of longer than 5 years was found in 60% of those with duodenal ulceration, in no patient with gastric cancer, and in under 50% of those with gastric ulcer and non-ulcer dyspepsia (Table XX).

The length of dyspeptic history was analysed according to the presence or absence of atrophic gastritis (Table XXI). Overall, a higher proportion of those patients with atrophic gastritis (73%) had a history of under 5 years, than did those with normal mucosa (55%).

It was felt that the symptoms attributable to ulcer or carcinoma might impose a bias upon the part played by atrophic gastritis in symptomatology. If the 40 cases of non-ulcer dyspepsia are analysed separately, it is seen that the bias in favour of a shorter history for those with atrophic gastritis suggested in the study of all the cases taken together, is reversed. Seventy-three per cent of non-ulcer dyspepsia

Diagnosis	No.	Duration of dyspeptic symptoms				
		0-1 yr.	1-5 yr.	5-10 yr.	10-20 yr.	over 20 yr.
Duodenal ulcer	22	3 (14%)	5 (23%)	8 (36%)	1 (4%)	5 (23%)
Gastric ulcer	21	10 (48%)	4 (19%)	4 (19%)	2 (9%)	1 (5%)
Gastric cancer	23	15 (65%)	8 (35%)	0	0	0
Non-ulcer dyspepsia	40	16 (40%)	9 (22%)	8 (20%)	3 (8%)	4 (10%)
Pernicious anaemia	9	4 (44%)	4 (44%)	1 (12%)	0	0
Total	115	48 (42%)	30 (26%)	21 (18%)	6 (5%)	10 (9%)

Table XX: The duration of dyspeptic history related to the diagnosis (percentages are taken to the nearest whole number).

Diagnosis		Duration of dyspeptic symptoms	
		Under 5 years	Over 5 years
Duodenal ulcer	17 normal	5 (29%)	12 (71%)
	5 atrophic	3 (60%)	2 (40%)
Gastric ulcer	6 normal	4 (80%)	2 (20%)
	15 atrophic	10 (66%)	5 (33%)
Gastric cancer	2 normal	2 (100%)	0
	17 atrophic	17 (100%)	0
Non-ulcer dyspepsia	15 normal	11 (73%)	4 (27%)
	25 atrophic	14 (56%)	11 (44%)
Pernicious anaemia	9 atrophic	8 (88%)	1 (12%)
	normal	0	0
Total	normal	22 (55%)	18 (45%)
	atrophic	52 (73%)	19 (27%)

Table XXI: The duration of dyspeptic symptoms, under and over 5 years, summarised from Table XX.

patients with normal mucosa had a history of under 5 years as compared with 56% of those with atrophic gastritis. A similar ratio is found in the gastric ulcer group, where 80% of those with normal mucosa had had symptoms for less than 5 years, compared with 66% of those with atrophic gastritis. Only in the cases of duodenal ulceration did it appear that the presence of atrophic gastritis was associated with a shorter history than that obtaining in those with normal mucosa. In the cases of gastric carcinoma, no case had a dyspeptic history of longer than 5 years.

Family history A family history of gastric carcinoma was obtained from 11 of the 115 subjects. No patient with duodenal or gastric ulcer admitted to, or was aware of, gastric carcinoma in the family, but such a history was given by 7 of those with non-ulcer dyspepsia, 3 with gastric carcinoma and one with P.A.

A family history of pernicious anaemia was found in 6 patients, 3 with non-ulcer dyspepsia, 1 with carcinoma and 2 with P.A., while a family history of goitre was obtained with one case with non-ulcer dyspepsia (Table XXII).

Comparing these records with the gastric histology, 10 of the 11 cases with a family history of gastric carcinoma had atrophic gastritis, an incidence of 14.1%. Applying the x^2 test to these figures, a significant variation from the expected incidence was found. Five of the 6 patients with a family history of P.A. had atrophic gastritis, as had the only patient with a family history of goitre. These findings, though suggestive of an aetiological relationship, did not differ significantly from the expected incidence using the x^2 test (Table XXIII).

Social history Of the 115 patients studied, 105 originated in Wales, 70% in a working class environment and 30% of middle class. The distribution of the classes in the disease groups and according to gastric histology, did not vary significantly from the overall distribution.

Diagnosis		Family History: Gastric carcinoma	Pernicious anaemia	Goitre
Non-ulcer dyspepsia	(40)	7 (17.5%)	3 (7.5%)	1 (2.5%)
Duodenal ulcer	(22)	0 (0%)	0	0
Gastric ulcer	(21)	0 (0%)	0	0
Gastric carcinoma	(23)	3 (13.0%)	1 (4.3%)	0
Pernicious anaemia	(9)	1 (11.0%)	2 (22%)	0

Table XXII: The incidence of gastric carcinoma, pernicious anaemia and goitre in the family history of patients in each diagnostic group.

Family History	Gastric mucosal histology: Non-atrophic (40)	Atrophic (71)	
Gastric carcinoma	1 (2.5%)	10 (14.1%)	$x^2 = 6.15$, $p < 0.02$
Pernicious anaemia	1 (2.5%)	5 (7.0%)	$x^2 = 0.93$, $p > 0.2$
Goitre	0 (0.0%)	1 (1.4%)	$x^2 = 0.52$, $p > 0.2$

Table XXIII: The incidence of gastric carcinoma, pernicious anaemia, and goitre occurring in the family history of patients with non-atrophic and with atrophic gastric mucosa.

Smoking The smoking and drinking habits of the patients studied are analysed in Table XXIV. It will be seen that there was a substantially higher proportion of non-smokers and non-drinkers in the carcinoma, non-ulcer dyspepsia and P.A. groups than among those with peptic ulcer. When the smoking and drinking habits are compared with mucosal histology (Table XXV), 45% of those with atrophic gastritis were non-smokers and 52% non-drinkers, compared with 17% and 37.5% subjectively of those with non-atrophic mucosa. In view of the well-recognised association between smoking and alcohol and peptic ulceration, those with non-ulcer dyspepsia were analysed separately, being a more comparable group (Table XXVI). Fifty-six per cent of those in this group with atrophic gastritis were non-smokers and 4% heavy smokers, compared with 20% and 20% respectively of those with non-atrophic mucosa. A less striking but similar trend was found with respect to alcohol intake, 68% of those with atrophic gastritis being non-drinkers and none regular drinkers, compared with 47% and 20% respectively of those with non-atrophic mucosa.

Clinical examination Clinical examination of the patients was unrewarding. Apart from the finding of an epigastric mass, enlarged liver or ascites in some of the cases of carcinoma, epigastric tenderness was an almost universal finding in all cases of both peptic ulcer and non-ulcer dyspepsia. Evidence of anaemia was present in some members of all groups. It was concluded that, while an essential part of any patient's investigation, physical examination had little to offer in helping to reach a diagnosis in a case of dyspepsia.

Diagnosis	No.	Smoking			Alcohol		
		0 - Occ.	10 - 20	20	0 - Occ.	Mod.	Regular
Duodenal ulcer	22	4 (18%)	14 (64%)	4 (18%)	6 (27%)	14 (64%)	2 (11%)
Gastric ulcer	21	4 (19%)	12 (57%)	5 (24%)	8 (38%)	10 (49%)	3 (14%)
Gastric cancer	23	11 (48%)	9 (39%)	3 (13%)	12 (52%)	10 (43%)	1 (4%)
Non-ulcer dyspepsia	40	17 (43%)	19 (47%)	4 (10%)	24 (60%)	13 (32%)	3 (7%)
Pernicious anaemia	9	8 (88%)	1 (11%)	1	8 (88%)	1 (11%)	1

Table XXIV: The smoking and alcohol habits of the patients studied.

		Smoking			Alcohol		
	No.	0-0cc.	10-20	20	0-0cc.	Mod.	Regular
Non-atrophic mucosa	40	7 (17%)	26 (65%)	7 (17.5%)	15 (37.5%)	21 (52%)	4 (10.5%)
Atrophic mucosa	62	28 (45%)	26 (42%)	8 (13%)	32 (52%)	25 (40%)	5 (8%)

Table XXV: The smoking and alcohol habits of 102 patients compared with the histological appearances of the gastric mucosa. (9 cases of pernicious anaemia, and 4 in whom gastric histology was not available, are excluded).

		Smoking			Alcohol		
	No.	0-0cc.	10-20	20	0-0cc.	Mod.	Regular
Non-atrophic mucosa	15	3 (20%)	9 (60%)	3 (20%)	7 (47%)	5 (33%)	3 (20%)
Atrophic mucosa	25	14 (56%)	10 (40%)	1 (4%)	17 (68%)	8 (32%)	1

Table XXVI: The smoking and alcohol habits of 40 patients with non-ulcer dyspepsia compared with the histological appearances of the gastric mucosa.

DISCUSSION

The term 'dyspepsia' is defined in the Shorter Oxford Dictionary as 'difficulty or derangement of digestion' and the inexactitude of this definition is matched only by the vagueness with which many patients describe their dyspeptic symptoms. In this study, although pain was complained of by 82% of the subjects, it tended to be more localised and severe in those with peptic ulcer, and more specifically related to meals, than in those with non-ulcer dyspepsia. Generally speaking, it was most distinct and periodic in the duodenal ulcer patients than in the remainder. Nausea was often accompanied by epigastric fullness in the non-ulcer dyspeptic group but this was also a feature of those with gastric ulcer and carcinoma and was found with equal frequency in patients with non-atrophic gastric mucosa and those with atrophic gastritis. Vomiting has many causes, but was found with equal frequency in those with duodenal ulcer, non-ulcer dyspepsia and cancer, though less commonly with gastric ulceration. It was found with approximately equal frequency in the presence of non-atrophic mucosa, and atrophic gastritis. Vomiting is not generally thought of as a frequent symptom of uncomplicated duodenal ulcer but Coghill (1967) records the finding of this symptom in between a quarter and a third of such patients. This symptom was complained of by 55% of the duodenal ulcer patients in this study, in none of whom were complications present other than occult bleeding. Weight loss, especially in the presence of a short history, is suggestive of carcinoma, but once again this symptom was found in 57% of the whole group of patients. Though commonest in those with carcinoma, it was complained of by a significant proportion of every group. Wood and Taft (1958) claim that the symptoms of chronic atrophic gastritis show a distinctive pattern and vary but little from patient to patient, a

view not held by Edwards and Coghill (1967), who, however, consider that it may give rise to dyspepsia, however ill-defined. From this study, no pattern of symptomatology has emerged which might help in the differentiation between ulcer, cancer and non-ulcer dyspepsia, or in the identification of atrophic gastritis. It might be said, in fact, that it has rather underlined the pleomorphism of the symptomatology of the various gastroduodenal diseases amongst which there is such an overlap of symptoms as to render accurate diagnosis on history alone often an impossibility.

In those cases of gastric ulcer and non-ulcer dyspepsia, those with atrophic gastritis had, overall, a longer history than those with normal mucosa, suggesting in the latter group at least that this may indicate that atrophic gastritis played a part in the symptomatology. Against this, however, it is seen that, despite an overwhelming preponderance of atrophic gastritis in the carcinoma group, no case had a dyspeptic history in excess of 5 years, the majority being under a year. It is clear from this finding that if atrophic gastritis has a causative relationship with gastric carcinoma, it is not likely to give rise to symptoms which might lead towards the identification of a 'high risk' pre-cancerous group of patients. The only other significant finding from this analysis is the preponderance of long history in the duodenal ulcer group when compared with those with gastric ulcer and non-ulcer dyspepsia. As these patients were all over 40 years of age, this probably is simply a reflection of the differences in age of onset of the conditions. Doig and Wood (1952) recorded in a large study that the symptoms of duodenal ulcer commenced, on average, in the mid-thirties, while those of gastric ulcer and atrophic gastritis began a decade later.

Family history The association between atrophic gastritis and gastric carcinoma has already been discussed in an earlier chapter, as has its association with pernicious anaemia. The autoimmune inter-relationships between gastritis and thyroid disease have likewise been reviewed. It was for these reasons that the family history with particular reference to gastric carcinoma, pernicious anaemia, and thyroid disease, was investigated. Flood (1958) found a history of carcinoma of the stomach in the relatives of patients with pernicious anaemia to be as high as the occurrence of carcinoma in the patients themselves, but there does not appear to be any reference in the literature to a similar study in relation to simple atrophic gastritis. In this study, one of the small group of 9 cases of pernicious anaemia had a family history of gastric cancer, as had 9 (14.5%) of 62 patients whose gastric mucosa revealed the changes of atrophic gastritis. Excluding those in whom atrophic gastritis was associated with gastric cancer, 7 of 45 (15.5%) of cases of simple atrophic gastritis had a family history of gastric carcinoma. These figures, taken either separately or in conjunction, indicate an incidence significantly in excess of the expected population incidence. Whether relevant or not, it is of interest to record that every case with a family history of gastric cancer was found to have intestinal metaplasia on gastric biopsy.

Of the 9 cases of pernicious anaemia, a family history of pernicious anaemia was found in 9%, which is in accord with the genetic background of the disease. The incidence of pernicious anaemia in the family history of the 62 cases of simple atrophic gastritis was 5 (4%) of whom one case had parietal cell antibodies. This figure does not differ significantly from the expected incidence, nor does the incidence of thyroid disease in the family history in

1.6% of this group.

Social history The relationship between smoking and peptic ulcer has aroused much debate. The proportion of life-long non-smokers has been shown to be lower among peptic ulcer patients than among control patients, a proportion most marked amongst those with gastric ulcer (Avery Jones, Gummer and Lennard Jones, 1968). Gastric ulcers heal more quickly in patients who stop smoking (Doll, 1964) and smoking has been shown to increase the rate of gastric secretion (Pifer and Raine, 1959). Smoking is, however, so intimately associated with the 'ulcer diathesis' that no categorical conclusion can be drawn as to its place as an aetiological factor. In the current study, the proportion of non-smokers was significantly lower among the peptic ulcer group as compared with the remainder, and a similar pattern was found among the non-drinkers (Table XXIV).

Those patients with non-ulcer dyspepsia were analysed separately in order to eliminate the possible bias imposed by the ulcer patients for the reasons stated above, the pernicious anaemia patients on account of their genetic background, and the carcinoma patients. Edwards and Coghill (1966) included heavy smoking and drinking among the aetiological factors in chronic atrophic gastritis and Wood and Taft (1958) regard chronic alcohol excess as being frequently associated with gastritis, disagreeing with Palmer (1954) who doubts if chronic gastritis is ever the result of chronic alcoholism. In the present study, our findings would lend support to Palmer's view, only 8% of all cases with atrophic gastritis being regular drinkers, none in the non-ulcer dyspepsia group. In this group, 56% were non-smokers and 68% non-drinkers, compared with 20% and 47% respectively of those with non-atrophic mucosa associated with non-ulcer dyspepsia.

These results, therefore, suggest that smoking and alcohol play

little part in the genesis of atrophic gastritis. A similar conclusion is suggested with regard to gastric carcinoma from this study, in which, of 23 cases, 50%, were non-smokers and 50% non-drinkers.

CHAPTER 6

THE MEASUREMENT OF GASTRIC ACID OUTPUT

Introduction

The presence of acid in the gastric juice was first recorded by Reaumur (1752) who taught a tame buzzard to swallow and regurgitate perforated metal tubes containing articles of food, and showed that the gastric juice so obtained turned blue litmus paper red. Seventy-two years later Prout (1824), proved that gastric juice contained free hydrochloric acid, and postulated that the chloride radicle came from the salt of the blood, the sodium being left behind. Beaumont (1833), with his celebrated patient Alexis St. Martin, was able to observe via a traumatic gastric fistula the activity of gastric juices in vivo, on foods of differing composition and under differing physiological conditions of the subject. Von Leube (1883) first used a swallowed tube to study and analyse the gastric juice and Ewald (1891) with his pupil Boas, devised a standard 'test breakfast' and studied the response to it of gastric secretion. The 'fractional test meal', in common use until very recent years, was based upon Ewald's test breakfast. Following the ingestion of a standard meal of gruel or another carbohydrate preparation, gastric contents were aspirated every 15 minutes for 2 to 3 hours and the samples tested for acidity using two indicators, Topfer's (dimethylaminoazo benzene) for 'free' acid, and phenothalein for 'total' acid. This concept of 'free' and 'total' acid arose from a study of responses to test meals by Michaelis (1926) in which he considered that a proportion of the acid was buffered by the ingested meal and that the acidity below pH 3 could be attributed to free hydrochloric acid, that above this level being combined. It has been shown, however, that the titration curve of uncontaminated gastric juice is identical to that of hydrochloric acid, and that the terms 'free' and 'total' acid have little meaning and should be abandoned in favour of that of total titratable acidity (Bock, 1962). The results

of fractional test meals in clinical practice were plotted on a printed paper graph against the 'normal range' in units which was based upon the acidity curves of 80 of 100 normal medical students studied by Bennett and Ryle (1921). The test, however, is neither precise, quantitative nor reproducible (Lawrie and Forrest, 1965) and has little diagnostic value.

That the test meal was a poor stimulus of gastric secretion was widely recognised from early in the present century and various agents were used to augment the secretory response - alcohol (Ehrmann, 1912), caffeine (Katsch and Kalk, 1924), histamine (Bockus and Bank, 1927). This latter agent, used either in conjunction with a test meal, or by itself in a dose of usually 0.5 mg given subcutaneously, produced a significant increase in the output of gastric acid evoked by a test meal, but the response had a wide variation in normal subjects and was of little routine diagnostic value (Polland, 1933). Histamine stimulates gastric acid secretion and increasing doses produce an increasing response until a maximum response is reached. Kay (1953) showed that a dose of 0.04 mg of histamine acid phosphate per kg body weight will produce maximal acid secretion in man and Marks, Komarov and Shay (1960) and Card and Marks (1960) showed that this dose resulted in maximum parietal cell activity when given either by a single injection or by continuous intravenous infusion; the response correlated closely with the number of parietal cells in the stomach, the 'parietal cell mass'. Thus, early work employing histamine in a dosage unrelated to body weight, while reproducible in an individual, gave no accurate estimate of parietal cell secretory capability, either when groups of subjects were compared or responses were studied in relation to disease status.

The concept of parietal cell mass as indicated by the maximal

acid secretory response is a valuable index of the state of the gastric body mucosa, its capability for acid production and its relation to disease processes. Submaximal doses of histamine, if related to body weight, are equally reproducible but while of value in experimental studies, have little relevance to the clinical situation. Kay (1953) further introduced the concept of gastric acid 'output', quantitating acid secretion in absolute terms as the product of acidity and volume in unit time in response to a secretory stimulus. Thus, for the first time, a reproducible means of testing maximal gastric secretion was available and Kay's augmented histamine test was used for a decade and a half as a reliable and valid index of human gastric secretory function. The administration of a secretory agent by single injection provides a pattern of acid output characterised by a rise, a peak, and a fall in volume and acidity and thus in calculating acid output, the peak output must be obtained, its duration known, and a calculation performed to provide an expression of acid output in mEq per hour. Various methods were adopted for achieving this - 15-45 minute output x 2 (Kay, 1953); 0-60 minute output (Card and Marks, 1960); two highest consecutive 15-minute peaks (Baron, 1963).

Adam, Card, Riddell, Roberts, Strong and Woolf (1954) first showed that histamine, given by continuous intravenous infusion in man, resulted in steady state levels of gastric acid secretion and permitted output to be calculated directly from the product of volume and acidity over a period of one hour. Dose response curves were constructed by this method, obviating the problem of the timing of peak responses found with single dose methods. Lawrie,

Smith and Forrest (1964) evolved the histamine infusion test, in which a maximal plateau response is obtained in response to the continuous intravenous infusion of histamine in a dose of 0.04 mg per kg per hour. This plateau response is continued for one hour, and these workers have shown that this dose produces a maximal acid output significantly higher than that obtained from the augmented histamine test.

The maximal response to histamine occurs within an hour but the side effects of this drug can be severe, and the need for an anti-histamine drug to prevent these has rendered this test unsuitable for easy outpatient use as well as being unpleasant for the patient. An analogue of histamine, Histalog (Betazole) (Rosiere and Grossman, 1951), does not have the side effects of histamine (but has its own) and does not require the addition of an anti-histamine drug. It does produce maximal acid secretion in a dose of 1.5 mg per kg (Burke and Whetsell, 1969) but this is not achieved within an hour and the test must be continued for up to 2 hours. It has never achieved popularity on this side of the Atlantic.

Gregory and Tracy (1961; 1964) after painstaking work, isolated two preparations, Gastrin I and II, from the gastric antrum and showed that a mixture of these polypeptides would elicit steady state secretion of acid in the dog. Makhlouf, McManus and Card (1964) showed that Gastrin II would produce a closely similar acid response to histamine in man, when given either by single injection or by intravenous infusion, and that the preparation produced only very slight side-effects in a

dose of 2 ug per kg. A number of synthetic peptides have been prepared, many of which have similar physiological actions to gastrin, the active principle being in the C terminal tetrapeptide. One of these, marketed as pentagastrin (Peptavlon, I.C.I. 50, 123) has been extensively investigated and has been shown to produce an acid secretory response in the stomach closely resembling that obtained in response to histamine (Multicentre Pilot Study, 1967) when given in a dose of 6 ug per kg either by single injection or by intravenous infusion. The side effects with this dose by either route are absent or only minimal, and the maximal response occurs earlier than with histamine, within 30 minutes in 74% of subjects (Multicentre Study, 1969) when given by intramuscular injection.

MATERIAL AND METHODS

The secretory capacity of the stomach was estimated using the intramuscular pentagastrin test described by Johnston and Jepson (1967). The test was carried out upon each patient in the group under study, and each was personally supervised by the author.

The tests were carried out in the morning, following an overnight fast. With the patient seated in a chair, the mucosa of the nose and nasopharynx was sprayed with approximately 100 mg of lignocaine solution, administered as an aerosol ('Xylocaine' aerosol, Astra-Hewlett Ltd.), the patient being encouraged to sniff vigorously and swallow in order to spread the solution over the pharyngeal wall. It was found that if the throat itself was sprayed, patients often experienced difficulty in subsequently swallowing the tube. After three to four minutes, a size 14 or 16F plastic nasogastric tube ('Portex') was passed via the nostril into the pharynx, the patient then being encouraged to swallow with the minimum of assistance from the operator. When the tube was satisfactorily in the

stomach, the stomach was aspirated to dryness by syringe, and the patient then placed in the left lateral position on a couch. Syringe aspiration was repeated in this position, and the tube then connected to a flask at the side of the couch. To a side tube on the flask was connected a line to a low pressure electric pump which exerted a suction of between 5 and 10 cm of water. The position of the tube, and, when necessary, that of the patient, were adjusted until a satisfactory flow of basal juice was obtained, and the tube then fixed to the patient's cheek or forehead with adhesive plaster. Continuous suction was then maintained for the duration of the test with frequent brief interruptions and the injection of a few millilitres of air down the tube, to minimise the risk of incomplete collection of juice due to blockage by mucus or by mucosa being sucked into the side holes of the tube.

Basal secretion of gastric juice was collected for a period of fifteen minutes, at the end of which period the juice collected was emptied out of the collecting flask and the test commenced. Pentagastrin (I.C.I. 50, 123 - 'Peptavlon') was injected by deep intramuscular injection into the deltoid muscle in a dose of 6 micrograms per kilogram body weight. Aspiration was continued for ten minutes, at the end of which time the juice collected was emptied from the flask and discarded. The test was continued for a further twenty minutes and the juice obtained at the end of that period, that is between ten and thirty minutes after injection of pentagastrin, was collected for measurement of volume and acidity. At the conclusion of the test, the tube was withdrawn and the patient allowed to return to the ward.

The aspirate obtained between ten and thirty minutes after injection was measured in millilitres. A 10 ml aliquot was pipetted into a small beaker and titrated to pH 7 with 0.1 N sodium hydroxide,

with constant magnetic stirring, using an electrometric pH meter and automatic titrator (Radiometer TTT 1C Model). From the volume of NaOH used, the concentration of acid in milliequivalents per litre was calculated. The output of acid secreted by the stomach in mEq/unit time was calculated from the product of the volume (in litres) and the concentration (in mEq/l). The output of acid during the twenty-minute period was thus obtained, and was multiplied by three to give the output in milliequivalents per hour. In those instances in which the pH of gastric juice lay between pH 6 and 7, achlorhydria was presumed and the acid output recorded as 0.

Example: A normal solution of HCl contains 1000 mEq/litre and is neutralised by an equal volume of normal NaOH.

Where x is the volume (ml) of 0.1 NaOH required to neutralise 10 ml of gastric juice, and y the total volume (ml) of gastric juice in the 20-minute aspirate:

10 ml gastric juice is neutralised by x ml 0.1 NaOH

1000 ml " " " " " 100x ml 0.1 NaOH

or by 10x ml N. NaOH

Therefore concentration of HCl = 10x mEq/litre

Output of HCl = $\frac{y}{1000}$ x 10x mEq in 20 minutes

or 3 $(\frac{yx}{100})$ mEq/hour.

Validity of the pentagastrin test

The validity of the pentagastrin test, and its reliability as an index of gastric secretory capacity, was tested in the following ways. Firstly, the results of the test were compared with the results of two accepted tests of gastric secretory capacity, namely the augmented histamine test (Kay, 1953), and the histamine infusion test (Lawrie, Smith and Forrest, 1964). Secondly, by a comparison of acid output values obtained by this test, and by the histamine infusion

test, in a large group of patients with gastro-duodenal disorders, and in normal subjects.

Comparison with histamine infusion test and augmented histamine test

Fifty-one patients were investigated. They were chosen randomly, no attempt being made to characterise the response to any particular disease state. Each subject had two tests, one with pentagastrin, 6 ug per kilogram intramuscularly, and the other with either histamine by intravenous infusion, 40 ug per kilogram per hour (26 tests), or histamine by subcutaneous injection, 40 ug per kilogram (25 tests). The tests were done in random order, separated by between one and three days, and all were personally supervised.

Histamine infusion test This was carried out by the method described by Lawrie, Smith and Forrest (1964). After an overnight fast, a size 14 or 16F nasogastric tube was passed as already described, and the test performed with the patient lying in the left lateral position. A 'Baxter' paediatric scalp vein needle was inserted into a vein on the back of the hand and an intravenous injection of 25 mg mepyramine maleate ('Anthisan') given by this route. A solution of histamine acid phosphate was made up, and diluted in 0.9% sodium chloride solution to a concentration determined by the patient's body weight which would give a dose of 40 ug per kilogram per hour when injected at a constant rate by continuous infusion pump. A syringe containing this solution was placed in a 'Palmer' continuous infusion pump, and connected to the scalp vein needle by a 'Baxter' fine plastic connecting tube. Following the commencement of the infusion, continuous aspiration was carried out as already described, and successive fifteen-minute samples collected. Each was measured, the concentration of HCl determined by titration with 0.1 NaOH to pH 7, and the output of HCl per 15 minutes calculated.

During the first three or four collections, the volume and concentration of acid gradually rose until they reached a steady state. The infusion was continued until a complete hour of 'steady state' secretion had been obtained, at which point the test was stopped. The sum of the outputs in the last four samples gave the output of acid in milliequivalents per hour. Twenty-six such tests were carried out.

Augmented histamine test This was carried out by the method described by Kay (1953). After preparation, nasogastric intubation, and positioning of the patient as described above, 50 mg mepyramine maleate ('Anthisan') was given by intramuscular injection. Thirty minutes later, histamine acid phosphate was given by subcutaneous injection in a dose of 40 ug per kilogram body weight. Gastric juice was collected by continuous aspiration, and successive ten-minute samples collected over a period of one hour, measured and titrated as described above. The three consecutive specimens with the highest outputs were taken to represent the peak half-hour output (Baron, 1963) and this was multiplied by two to give the output of acid in milliequivalents per hour. Twenty-five such tests were carried out.

Pentagastrin test This was carried out in an identical manner to that already described, fifty-one such tests being carried out.

RESULTS

The degree of agreement between the acid outputs obtained in response to intramuscular pentagastrin, and to histamine by intravenous infusion or subcutaneous injection, has been assessed by analysis of the mean difference between the outputs in each pair of tests, employing Student's 't' test (Table XXVII). When comparing the mean outputs obtained with pentagastrin and with histamine by infusion, the former

No. of tests	Test for comparison Agent	Acid output (Y) (Mean S.E.)	I.M. Pentagastrin Acid output (X) (Mean S.E.)	Differences between tests Y - X (Mean S.E.)	't'	'p'
26	H.I.T.	24.17 (3.42)	21.84 (3.33)	2.33 ($\pm$ 4.77)	0.488	>0.6
25	A.H.T.	29.73 (2.84)	30.72 (2.95)	-0.99 ($\pm$ 4.09)	0.091	>0.9

Table XXVII: Comparison between the peak acid outputs obtained employing the histamine infusion test (H.I.T.) and augmented histamine test (A.H.T.) and the intramuscular pentagastrin test.

were lower, the mean difference being 2.33 mEq/hr., this difference, however, not reaching statistical significance ($p > 0.6$). The mean output obtained with pentagastrin when compared with histamine subcutaneously was, on the other hand, slightly higher, by only 0.99 mEq/hr., again an insignificant difference ($p > 0.9$). Correlation coefficients were calculated from the results of the pairs of tests, and linear regression equations computed. Comparing pentagastrin with histamine infusion, a correlation coefficient of 0.87 was found, the regression equation being $Y = 0.897X + 4.572$ (Fig. 9). Comparing pentagastrin with subcutaneous histamine, the correlation coefficient was 0.95, and the regression equation $Y = 0.982X - 0.957$ (Fig. 10). The correlations obtained in both instances were highly significant ($p < 0.001$).

Comparison with histamine infusion test in disease states and normal subjects

Intramuscular pentagastrin tests were carried out on 154 subjects employing the methods already described. Of these, 22 were normal subjects, with no history of digestive disorder or other disease process, and were volunteers. The remaining subjects were suffering from either duodenal ulcer (71), benign gastric ulcer (38), or gastric carcinoma (23). The results of the acid outputs obtained in these subjects by this test were compared with the acid outputs of a previously studied group obtained using the histamine infusion test. This group comprised 478 subjects investigated by Mr. James Lawrie of whom 104 were normal volunteers. The remaining subjects were suffering from duodenal ulcer (272), benign gastric ulcer (73), or carcinoma of the stomach (29). The ages of the subjects ranged from 17 to 78 years, and the sex distribution is shown in Figure 11 which shows the pattern of acid output in the two groups.

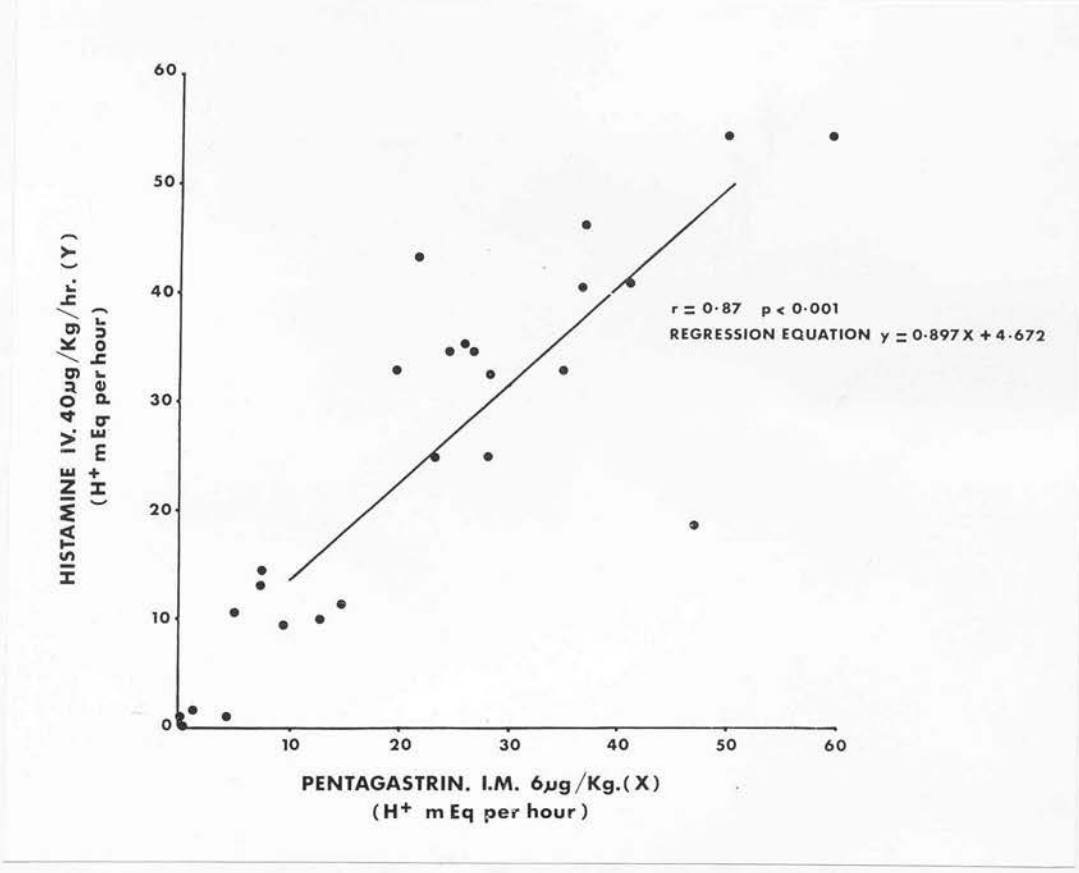


Figure 9: The correlation between the maximal acid output obtained in response to histamine, 40 ug per kg per hour by intravenous infusion and pentagastrin, 6 ug per kg by intramuscular injection.

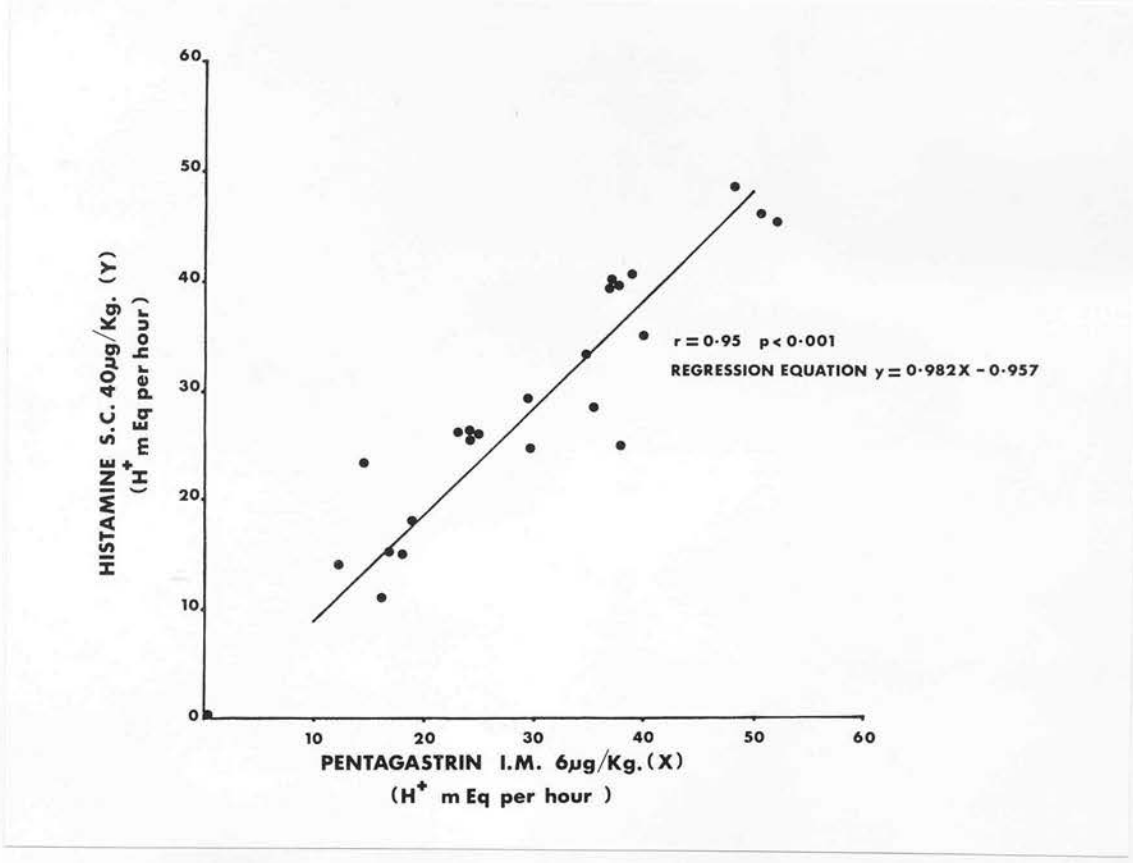


Figure 10: The correlation between the maximal acid output obtained in response to histamine, 40 ug per kig subcutaneously and pentagastrin, 6 ug per kg by intramuscular injection.

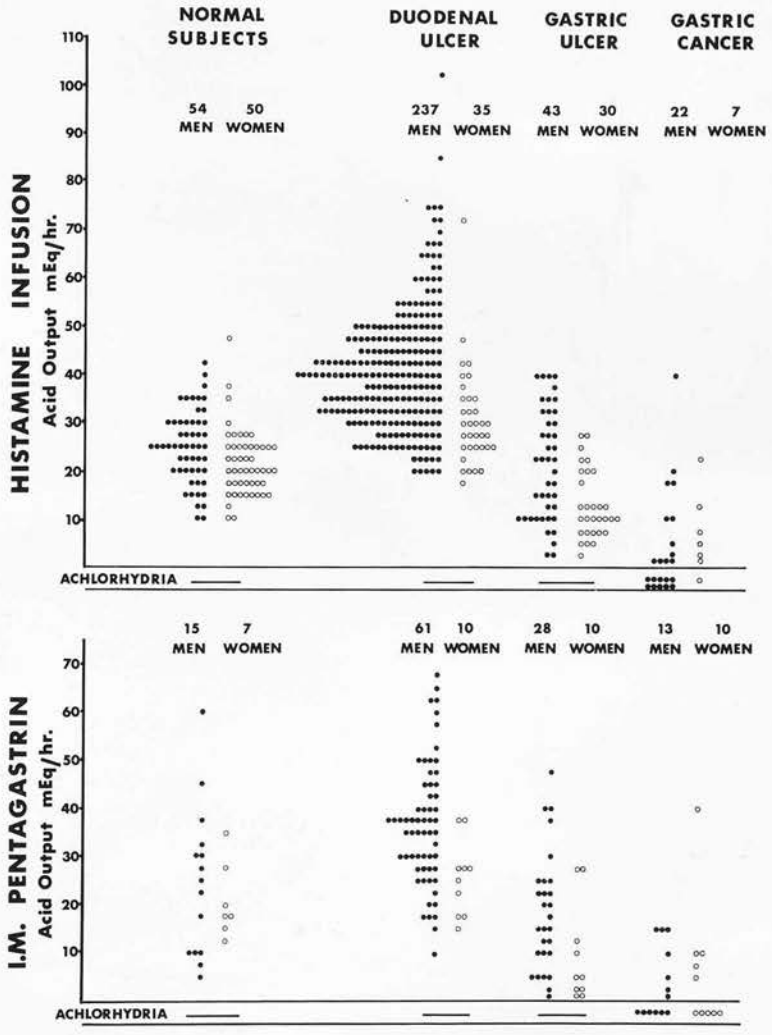


Figure 11: The pattern of acid output obtained in response to histamine 40 ug per kg per hour by intravenous infusion, and pentagastrin 6 ug per kg per hour, in 632 subjects.

For the purposes of analysis, the mean difference between the acid output in the two tests in each disease group was compared using Student's 't' test. In view of the differences between the numbers in each sample, the standard error of mean differences was calculated from the pooled variance. The discriminatory value of each test was assessed by comparison of the mean differences between the outputs of acid in each disease group, with those found in normal subjects.

The pattern of acid output following both stimuli was found to be similar in each disease group, as will be seen from a study of Figure 11, and Table XXVIII. Analysis of the mean differences in acid output following pentagastrin and histamine in each group indicates that the output following pentagastrin was consistently lower than that following histamine, as is shown in the table, but these differences reached significance only in the case of male patients with duodenal ulcer. When the mean differences between the acid outputs of those with gastroduodenal disease and normal subjects were compared, differences were observed between normal subjects and patients with duodenal ulcer, normal subjects and patients with gastric ulcer, and normal subjects and patients with gastric carcinoma with both tests. These comparisons are shown in Table XXIX, and it will be seen that the differences found were significant except in the case of female patients with duodenal ulcer, and male patients with gastric ulcer, when pentagastrin was used as the stimulant. The differences were of greater magnitude with histamine than with pentagastrin in all cases.

Discussion

It has previously been shown (Kay, 1953; Lawrie, Smith and Forrest, 1964) that the augmented histamine test, and the histamine infusion test are reproducible, and provide a valid estimate of the secretory capacity of the stomach. It has further been demonstrated

	Pentagastrin				Histamine				Mean diff.	S.E.	t	p
	No.	Mean output (mEq/hr) HCl	S.D.	S.E.	No.	Mean output (mEq/hr) HCl	S.D.	S.E.				
Normals												
Male	15	25.1	15.7	4.05	54	25.3	7.6	1.03	0.2	± 2.87	0.069	>0.9
Female	7	20.6	7.9	3.00	50	21.7	6.9	0.97	1.1	± 2.83	0.388	>0.6
Duodenal ulcer												
Male	61	36.9	12.7	1.63	237	41.5	12.8	0.83	4.6	± 1.83	2.525	<0.02
Female	10	25.2	7.8	2.46	35	31.2	10.1	1.71	6.0	± 3.46	1.639	>0.1
Gastric ulcer												
Male	28	18.8	12.5	2.35	43	21.4	11.4	1.74	2.6	± 2.86	0.906	>0.3
Female	10	9.4	10.2	3.21	30	13.5	6.8	1.24	4.1	± 3.15	1.30	>0.1
Gastric carcinoma												
Male	13	4.8	6.4	1.78	22	5.9	10.2	2.17	1.1	± 3.15	0.349	>0.7
Female	10	6.9	12.4	3.93	7	7.4	8.3	3.14	0.5	± 5.40	0.09	>0.1

Table XXVIII: Mean acid outputs with intramuscular pentagastrin 6 ug per kg and histamine infusion 4 ug per kg per hour in 126 normal subjects, and 506 patients with gastric diseases.

		Mean difference from normals Mean diff. ± S.E.		t	p
Duodenal ulcer					
Male	Pentagastrin	+ 11.8	3.84	3.072	< 0.01
	Histamine	+ 16.2	1.79	9.050	< 0.001
Female	Pentagastrin	+ 4.6	3.86	1.191	> 0.2
	Histamine	+ 9.5	1.82	5.219	< 0.001
Gastric ulcer					
Male	Pentagastrin	- 6.3	4.36	1.440	> 0.1
	Histamine	- 4.2	1.93	2.172	< 0.05
Female	Pentagastrin	- 11.2	4.59	2.440	< 0.05
	Histamine	- 8.2	1.58	5.176	< 0.001
Gastric carcinoma					
Male	Pentagastrin	- 20.3	4.65	4.365	< 0.001
	Histamine	- 19.4	2.12	9.150	< 0.05
Female	Pentagastrin	- 13.7	5.34	2.565	< 0.05
	Histamine	- 14.3	2.84	5.035	< 0.001

Table XXIX: The discriminating value of intramuscular pentagastrin 6 ug per kg and histamine infusion 4 ug per kg per hour.

that pentagastrin in a dose of 6 ug/kg produces a gastric secretory response of HCl very similar to that obtained in response to histamine in a dose of 40 ug/kg when given by a single injection (Maklouf, McManus and Card, 1966), and comparable plateau responses are obtained from intravenous infusions of the two drugs with similar doses to the above (Multicentre Pilot Study, 1967). Following upon the evaluation of pentagastrin as a stimulant of gastric secretion, the intramuscular pentagastrin test has been evolved. In the original description of this test (Johnston and Jepson, 1967) it was shown that (a) by constructing dose response curves, the dose of 6 ug/kg produced a maximal acid response (b) the test was reproducible, and (c) the peak response occurred between 10 and 30 minutes after injection in 95% of 100 subjects tested.

From the results obtained in this study, the following conclusions are reached: (a) the intramuscular pentagastrin test gave results for peak hour acid output which compared closely with those obtained employing two other tests of proven value. While the output produced was slightly lower than that resulting from intravenous histamine, the correlation with the augmented histamine test was extremely close. (b) A close similarity was found between the results of this test in differing disease states and levels of acid output, and those obtaining with the histamine infusion test, the pentagastrin test giving a similar pattern of discrimination between normal patients and those with gastroduodenal disorders to that produced by the histamine infusion test.

The test was comparatively simple to conduct, was short in duration, and was free of side effects. It would therefore appear that not only does this test give a valid expression of the secretory capacity of the stomach, but has the merit of being pleasanter for

the patient. It would appear to be the method of choice for the measurement of gastric acid in routine clinical practice, when the detection of abnormally high or low levels of secretion is what is being sought.

ACID OUTPUT STUDIES

The intramuscular pentagastrin test was carried out on each of the 115 patients included in the study, of whom gastric biopsies were available for study in 111. No side effects or complications were experienced in these tests.

Results

Acid output related to gastric mucosal histology

The mean acid output of the 40 patients in whom non-atrophic mucosa was found was 29.4 mEq/hour, compared with a mean of 7.1 mEq/hour in the 71 patients whose mucosa exhibited the changes of atrophic gastritis. The range of acid outputs in the two groups is shown in Figure 12. The mean outputs of the non-atrophic and the atrophic group as a whole were compared using Student's 't' test and the difference found to be highly significant ($p < 0.001$). The subjects were then sub-divided into their respective groups according to the grade of mucosal change, each group being compared with the group next to it in order of severity (Table XXX). It will be seen from a study of this table that no significant difference existed between the acid output of those with normal mucosa and those with superficial gastritis and minor mucosal changes, i.e. those with non-atrophic mucosa. A significant difference was, however, found between the mean acid outputs of those with superficial gastritis and those with mild (grade 1 - 2) atrophic gastritis ($p < 0.05$) and between those with mild and those with moderate (grade 3 - 4) atrophic gastritis ($p < 0.05$). The difference between those with moderate and those with severe

	No.	Mean acid output (mEq/hr.)	S.E.	S.D.	Difference between pairs			
					Mean diff.	S.E.	't'	p
Non-atrophic mucosa (total)	40	29.40	2.75	17.4				
					22.3	3.0	7.43	<0.001
Atrophic mucosa (total)	71	7.10	0.84	10.1				
Normal mucosa	28	29.85	3.31	17.51				
					2.40	5.77	0.41	>0.5 <0.6
Superficial gastritis and minor changes	12	27.45	4.74	16.43				
					13.38	5.46	2.43	>0.02 <0.05
Mild atrophic gastritis grades 1-2	15	14.07	2.66	9.97				
					6.56	3.32	1.97	>0.02 <0.05
Moderate atrophic gastritis grades 3-4	26	7.41	2.02	10.5				
					4.36	2.51	1.73	>0.05 <0.1
Severe atrophic gastritis grades 4-5	26	3.04	1.52	7.88				
Gastric atrophy	4	0.0						

Table XXX: The mean acid outputs related to the state of the gastric mucosa in those with non-atrophic and atrophic mucosa taken as a whole, and sub-divided into the grades of mucosal change.

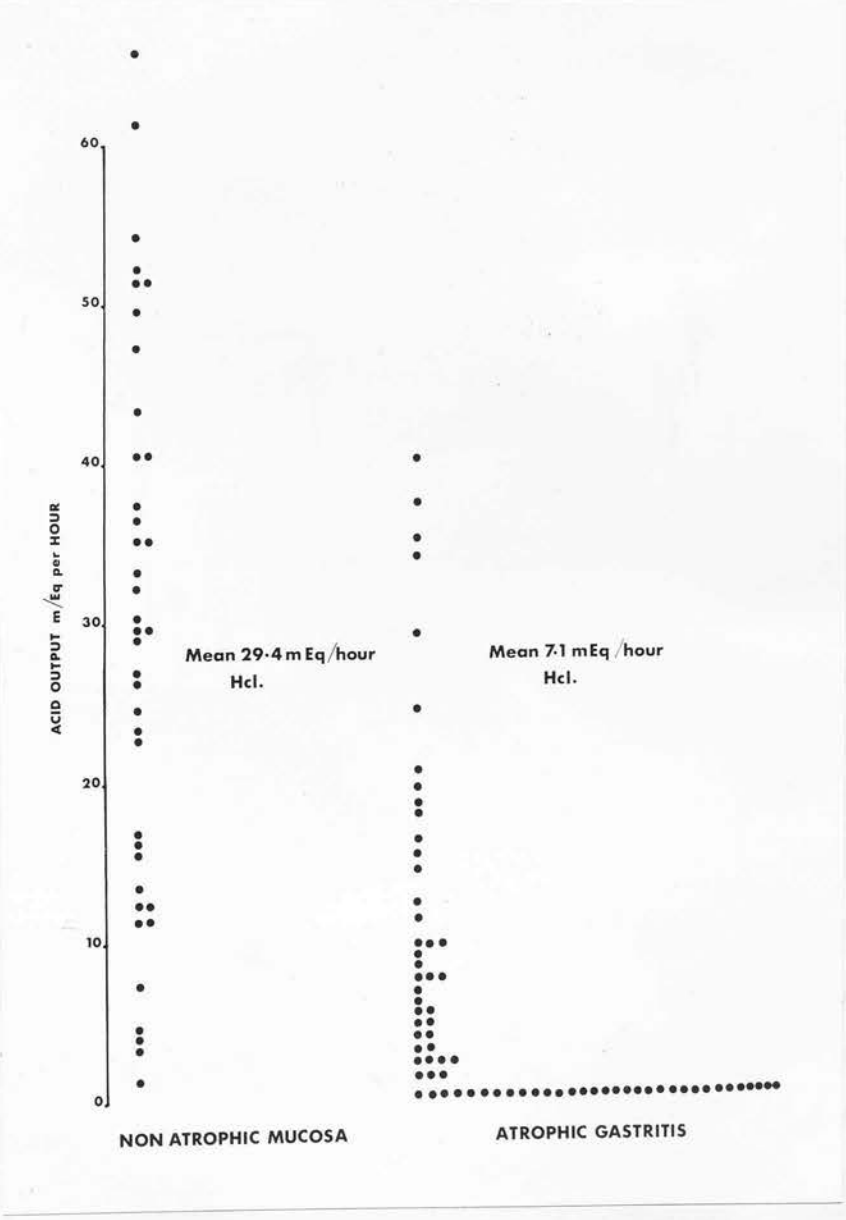


Figure 12: The range of acid output following pentagastrin 6 ug per kg in 40 subjects with non-atrophic mucosa, and 71 subjects with atrophic gastritis.

(grade 5 - 6) atrophic gastritis did not quite reach statistical significance however ($p < 0.1$). The output in this latter group did, however, differ significantly from all the other groups and a progressive diminution in acid output was seen with increasing severity of atrophic change (Fig. 13).

As has already been described, the incidence of intestinal metaplasia was 38% of the whole group of patients. It was found only in the presence of atrophic changes and occurred in 59% of those patients, its incidence increasing with the severity of the atrophic gastritis. This latter observation is reflected in the finding of a significantly lower mean acid output of 4.5 mEq/hour in those patients exhibiting intestinal metaplasia of their gastric mucosa when compared with the mean of 10.1 mEq/hour in those patients with atrophic gastritis but with no intestinal metaplasia (Table XXXI).

The correlation between the presence or absence of hypochlorhydria and the state of the gastric mucosa was investigated. An acid output of 10 mEq/hour or less is commonly regarded as indicating hypochlorhydria and, as such, should be expected to reflect the presence of gastric mucosal atrophy. Of the 40 patients with non-atrophic mucosa, 6 (15%) had an output of 10 mEq/hour or less, while of the 71 patients with atrophic gastritis, 15 (21%) had an acid output in excess of this level (Fig. 14). Looked at more closely with the subjects sub-divided into the six categories according to state of mucosa (Fig. 15), 21% of those with normal mucosa were hypochlorhydric but hypochlorhydria was not found in any patient with superficial gastritis. Of those with atrophic changes, the incidence of hypochlorhydria rose progressively with the severity of atrophy from 60% in those with mild atrophic gastritis to 100% in those with gastric atrophy. Those cases of atrophic gastritis with, and those without,

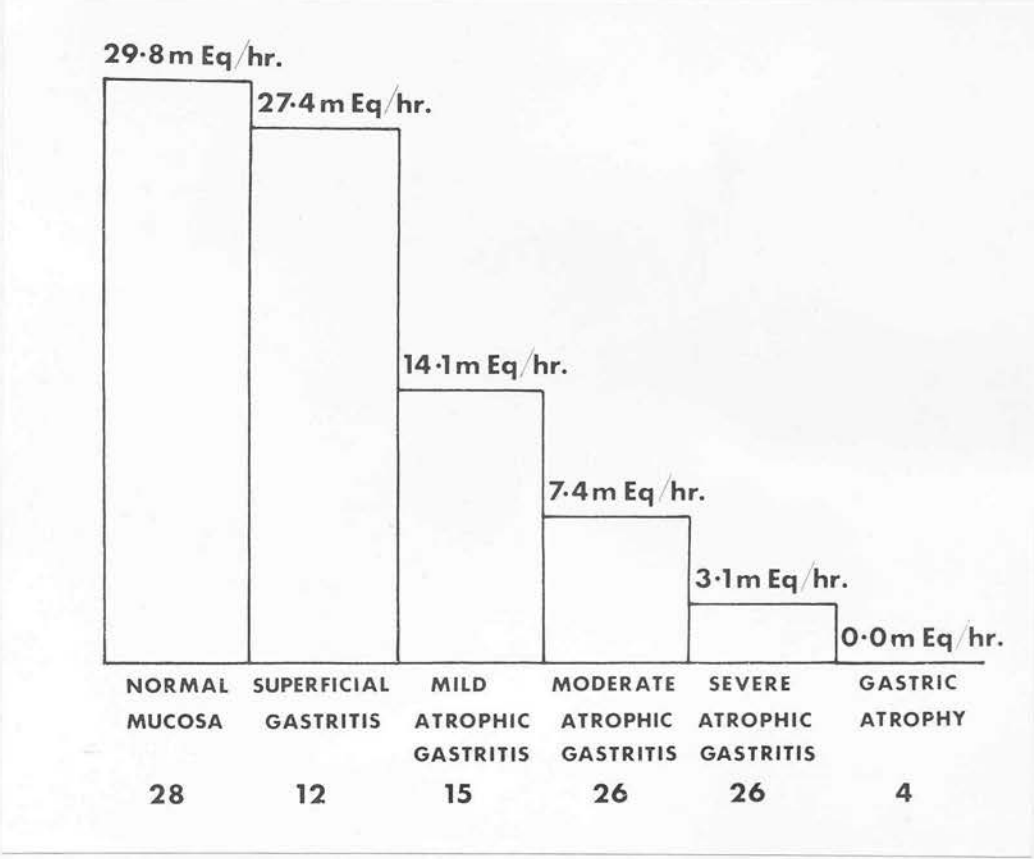


Figure 13: The mean acid output after pentagastrin related to the gastric mucosal histology.

	No.	Mean acid output (mEq/hr.)	S.E.	S.D.	Difference Mean diff.	S.E.	't'	p
Without intestinal metaplasia	29	10.1	1.97	10.6				
					5.61	2.39	2.43	<0.02 >0.01
With intestinal metaplasia	42	4.5	1.35	8.8				

Table XXXI: The mean acid output of those cases with atrophic gastritis with, and without, intestinal metaplasia.

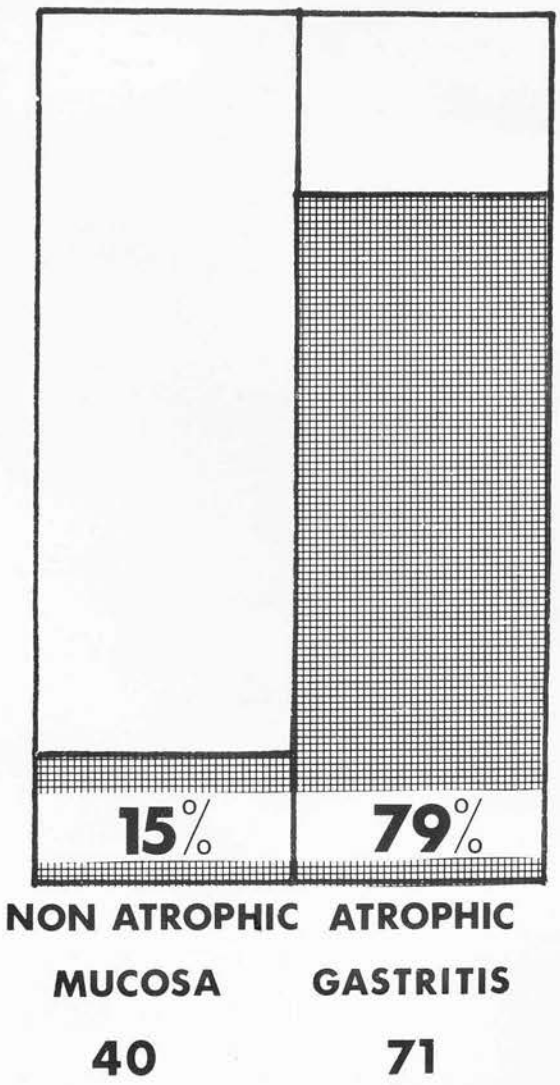


Figure 14: The incidence of hypochlorhydria in 40 subjects with non-atrophic gastric mucosa and 71 with atrophic gastritis. (The percentage incidence of hypochlorhydria is indicated by the hatched portion of each histogram).

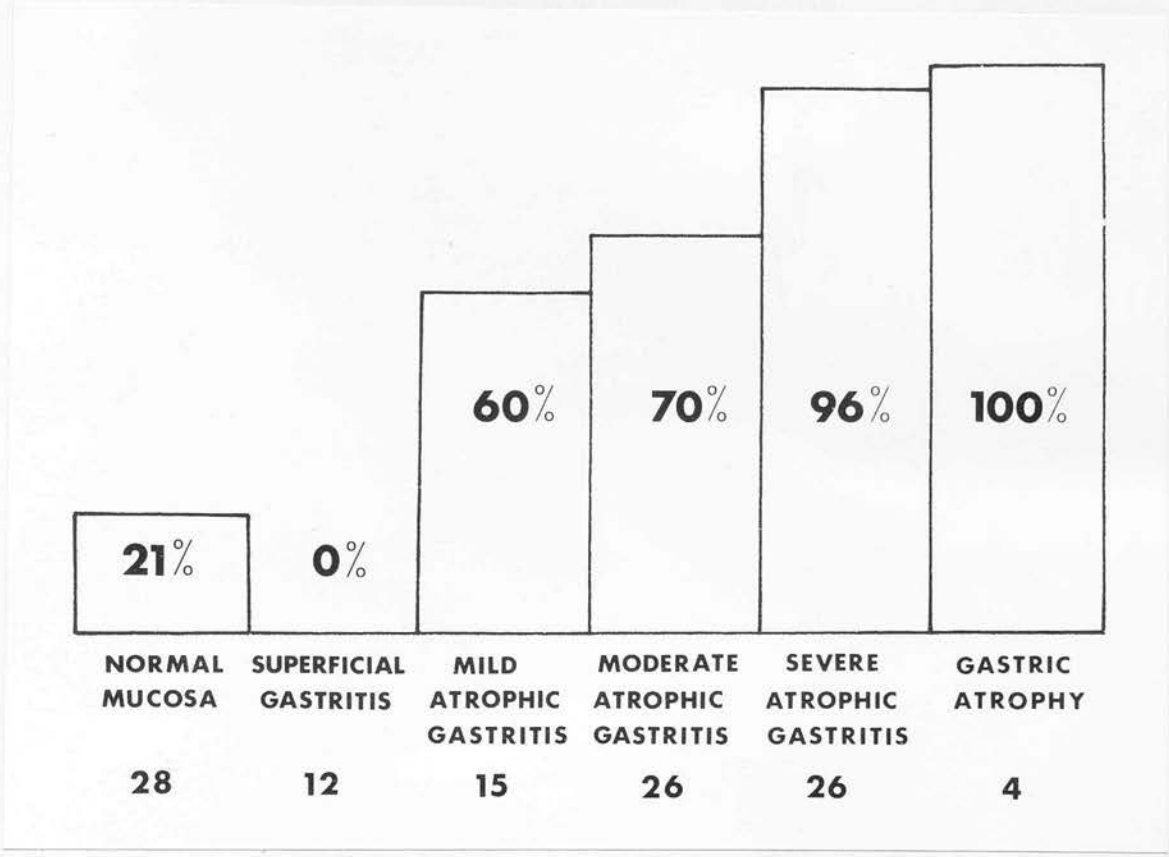


Figure 15: The incidence of hypochlorhydria related to the gastric mucosal histology in 111 subjects.

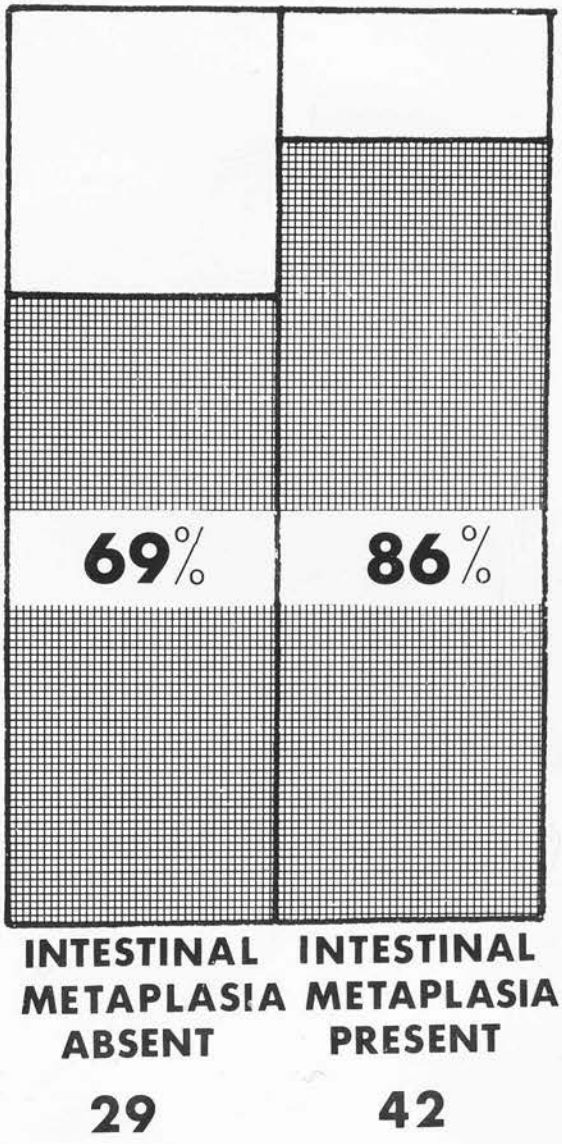


Figure 16: The incidence of hypochlorhydria in 71 subjects with atrophic gastritis, 42 with intestinal metaplasia and 29 without. (The percentage incidence of hypochlorhydria is indicated by the hatched portion of each histogram.

	No.	Mean max. H^+ conc. (mEq/litre)	S.E.	S.D.	Mean diff.	S.E.	't'	p
Non-atrophic mucosa	40	100.9	5.9	33.7				
					53.2	8.5	6.15	<0.001
Atrophic mucosa	71	47.7	5.5	41.0				

Table XXXII: The maximum concentration of H^+ obtained in response to 6 ug pentagastrin intramuscularly in subjects with non-atrophic, and atrophic mucosa.

intestinal metaplasia were studied in the same way. Hypochlorhydria was found in 86% of those with this change compared with 69% of those in whom it was not demonstrated (Fig. 16).

2. Acid concentration related to gastric mucosal histology

The mean maximal H^+ concentration of the gastric juice of 40 subjects with non-atrophic mucosa was 100.9 mEq/litre with a range of from 18 - 139 mEq/litre. In those with atrophic changes, the mean was 47.7 and range from 0.0 to 122 mEq/litre. The difference between these means was highly significant ($p < 0.001$) (Table XXXII). An H^+ concentration in response to maximal stimulation with pentagastrin of less than 100 mEq/litre was found in 12 (30%) of those with non-atrophic mucosa, and 65 (91%) of the 71 patients with atrophic change. In this latter group, all 6 who secreted acid of a concentration higher than 100 mEq/litre were patients with peptic ulcer - 2 duodenal and 4 gastric.

3. Acid output related to clinical diagnosis

The mean acid outputs and range of acid output values found in each disease group is shown in Table XXXIII and Figure 17 and the means were compared using Student's 't' test. No significant difference was found between the means of those with carcinoma and non-ulcer dyspepsia with atrophic gastritis, or between those with duodenal ulcer and non-ulcer dyspepsia with non-atrophic mucosa. Significant differences were found, however, between the acid output of those with duodenal ulcer and those with gastric ulcer ($p < 0.01$), carcinoma ($p < 0.001$) and non-ulcer dyspepsia with atrophic gastritis ($p < 0.001$); between non-ulcer dyspepsia without atrophy and gastric ulcer ($p < 0.05$), carcinoma ($p < 0.001$) and non-ulcer dyspepsia with atrophic gastritis ($p < 0.001$); and between gastric ulcer and carcinoma ($p < 0.001$) and non-ulcer dyspepsia with atrophic gastritis ($p < 0.001$).

	D.U.	G.U.	Ca.	N.U.D.		P.A.
				Non-atrophic	Atrophic	
Mean acid output (mEq/l)	34.5	14.1	5.4	25.3	3.2	0.0
Range	3.1 - 66.4	0.0 - 40.6	0.0 - 40.6	1.0 - 51.5	0.0 - 18.6	0.0
S.D.	16.3	10.74	9.26	16.65	4.62	0.0
S.E.	3.47	2.34	1.97	4.44	0.90	0.0
No.	22	21	23	15	25	9

Table XXXIII: The mean values and range of acid output in 115 patients sub-divided into disease groups.

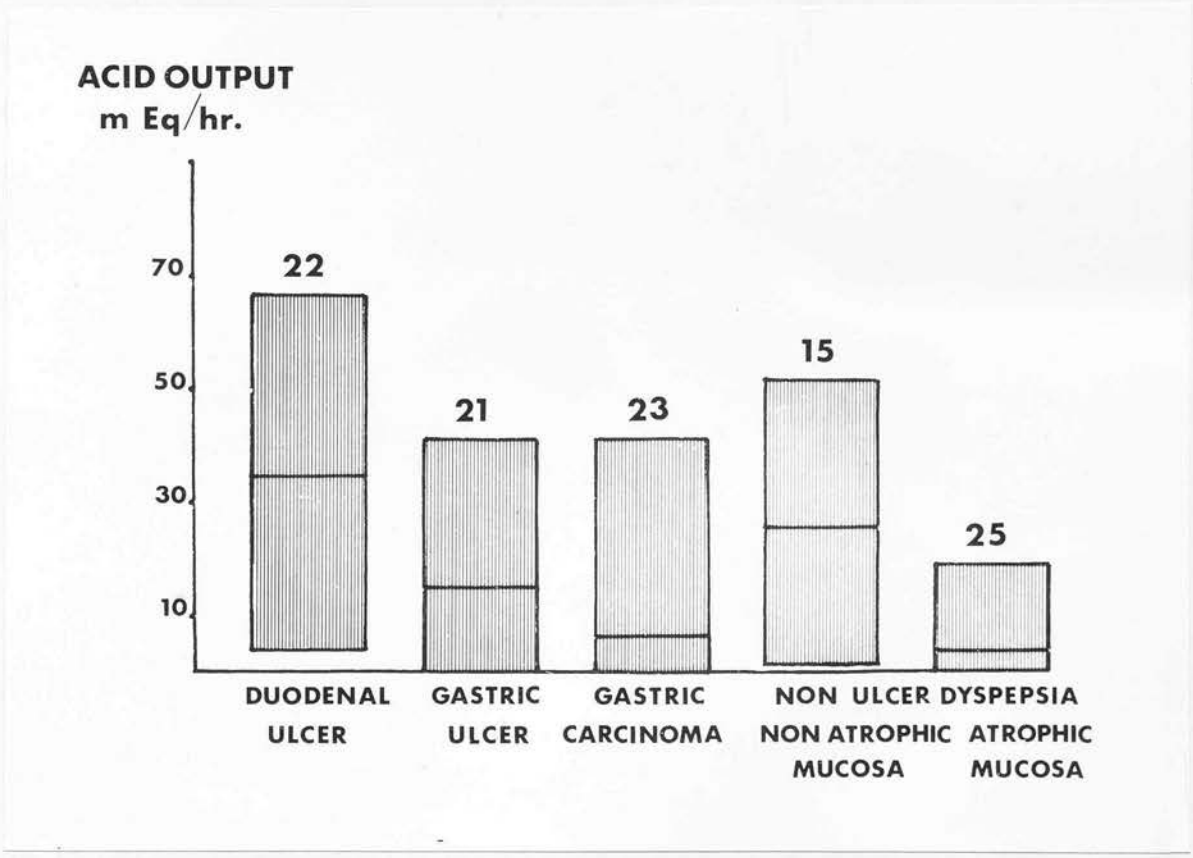


Figure 17: The means and ranges of acid output found in the disease groups studied.

Hypochlorhydria was found in 1 patient with duodenal ulcer (4.5%), 9 patients with gastric ulcer (43%), and 20 patients with carcinoma (87%). It was found in 67% of all those with non-ulcer dyspepsia, in 20% of those with non-atrophic and 96% of those with atrophic mucosa (Table XXXIV).

Discussion

No significant difference was found in the acid output in response to pentagastrin in a dose of 6 ug per kilogram, between patients with normal mucosa and those with superficial gastritis. This finding is in accord with that of Burhol and Myren (1968) but at variance with Bock, Richards and Witts (1963) and Christiansen and Johansen (1966), who both found a significant reduction in both acidity and output in their cases with superficial gastritis on maximal stimulation with histamine when compared with subjects with normal mucosa (Table XXXV). It is difficult to explain these conflicting findings except on the grounds of differences in interpretation of the biopsy findings where slight inflammatory and atrophic changes are found, as has been discussed in an earlier chapter. All these workers agree, however, that a significant reduction in acid output occurs in atrophic gastritis. The degree of hypochlorhydria correlates well with the severity of the atrophic change in Christiansen and Johansen's study in which they showed a significant difference between the mean acid output in those with mild atrophic gastritis (8.47 mEq/hour) and those with severe atrophic gastritis (1.92 mEq/hour). A similar pattern was found in the present study with steady reduction in the mean acid output with progressive severity of atrophic change. Despite this, the range of acid output in each group was considerable, indicating that normal or even high acid levels can be found in the presence of bioptically severe atrophic change.

Acid output	D.U.	G.U.	Ca.	N.U.D.		P.A.
				Non-atrophic	Atrophic	
10 mEq/hour	21	12	3	12	1	0
10 mEq/hour	1	9	20	3	24	9
Total	22	21	23	15	25	9

Table XXXIV: The number of patients in each disease group in whom the acid output was found to exceed or fall below 10 mEq per hour.

	Mean acid output (mEq/hour)			
	Normal mucosa	Superficial gastritis	Atrophic gastritis	Gastric atrophy
Bock, Richards and Witts (1963)	21.9 (36)	10.0 (25)	3.7 (22)	0.0 (14)
Christiansen and Johansen (1966)	22.7 (13)	10.8 (14)	4.1 (65)	0.0 (4)
Burhol and Myren (1968)	19.8 (44)	17.4 (47)	5.6 (46)	-
Present study	29.8 (28)	27.4 (12)	7.2 (67)	0.0

Table XXXV: The mean acid outputs following maximal stimulation with histamine in three published series compared with the present study, in relation to mucosal histology. (The figures in brackets are the number of subjects in each group).

Other workers, notably Davidson and Markson (1955), Joske, Finckh and Wood (1955) and Williams, Edwards, Lewis and Coghill (1957) have also described a close correlation between atrophic change and acid output, but their figures are not comparable with the present study as sub-maximal doses of histamine were used to stimulate acid production.

The incidence of hypochlorhydria in patients with atrophic mucosa in the present study was 79% compared with 86% in Christiansen and Johansen's study in 71 and 69 subjects respectively. They found hypochlorhydria in 26% of 27 patients with non-atrophic mucosa compared with 15% in the present study, although all but one of their hypochlorhydric patients in this group had superficial gastritis.

It is generally accepted that achlorhydria following maximal stimulation with histamine is an important feature of pernicious anaemia (Callender, Reteif and Witts, 1960). Hypochlorhydria or achlorhydria was found in the large majority of patients with atrophic gastritis. The finding of low acid output levels in the presence of normal mucosa, or high levels in the presence of atrophic gastritis, however, requires explanation. It has been shown (Kay, 1953) that the augmented histamine test gives consistently reproducible results in the same individual, and that there is a highly significant correlation between the maximal acid output obtained by this test, and the number of parietal cells in the stomach (Card and Sircus, 1958). As has already been discussed, the correlation between results in the augmented histamine and pentagastrin tests is very close indeed and it may be inferred that this latter test will also reflect the parietal cell population of the stomach. Hypochlorhydria therefore is an indication of a reduction in the number of functioning parietal cells, or in other words, an indication of gastric mucosal atrophy. Lack of correlation

between biopsy findings and acid output is likely therefore to indicate either an error in technique in the test of gastric secretion, or to indicate that the gastric biopsy is not representative of the gastric mucosa as a whole. Although, in this study, multiple biopsies usually showed the same histological features, a finding supported by many writers as has been already discussed, others, notably Shiner and Doniach (1957) and Christiansen and Johansen (1966), have stressed the importance of multiple biopsies in obtaining an accurate picture of the state of the gastric mucosa as a whole.

The highest acidity found in gastric juice is approximately 153 mEq/litre (Hollander and Cowgill, 1931; Gray, 1943). This closely approximates to the concentration of the electrolytes in the plasma, and suggests that the maximal acidity of gastric juice is dependent upon the plasma concentration of these electrolytes. Hollander (1932; 1938) considered that the acidity of the parietal cell secretion was constant, and that the maximal acidity of gastric juice was therefore a reflection of parietal cell secretory capacity. He considered that variations in the acidity of the juice was the result of dilution, and possibly neutralisation of the parietal cell secretion by an alkaline non-parietal cell secretion. Teorell (1932; 1933; 1947) while also considering the parietal cell secretion to be constant, held the view that variations in acidity of gastric juice were due to a subsequent back diffusion of H^+. He considered that on its secretion into the gastric glands, HCl dissociated into $H^+$and Cl- some of the former being re-absorbed across the mucosa, being replaced by metallic cations, principally Na^+, derived from the plasma. He considered that this ionic exchange was dependent upon the ionic concentration on each side of the mucosa, and that provided the permeability of the mucosa remained constant, the concentration of

H^+, Na^+ and Cl- of the gastric juice was directly related to the rate of parietal cell secretion. Jorres (1957) considered that these two hypotheses were not mutually exclusive, but thought that the ionic content of the non-parietal cell secretion was variable, while Makhlouf, McManus and Card (1966) considered that the non-parietal cell secretion had an identical composition to that of interstitial fluid, and that its volume was proportional to the size of the stomach, and therefore the area of its capillary bed.

In animal experiments using cats, Bond and Hunt (1956) showed that a fall in the output of H^+ occurred when the mucosa was damaged by the application of sodium fluoride. This fall in H^+ output was accompanied by a rise in the output of Na^+. Kay and Forrest (1956), and Blair and Forrest (1960) irrigated canine Heidenhain pouches with drugs of the anti-histamine type during histamine stimulation and showed a fall in H^+ secretion accompanied by the production of a juice rich in Na^+. When H^+ reappeared in the secretion, the output of Na^+ fell, the effect being attributed to irritation of the gastric epithelium with inhibition of parietal cell activity. In dogs with vagally innervated fundic pouches, Code, Higgins, Noll, Orvis and Scholer (1963) damaged the mucosa with a variety of agents (salicylates, urea, decyl sulphate). They showed that, by instillation of HCl into the damaged pouch, H^+ passed into the wall of the stomach, and this was accompanied by the secretion of a juice rich in Na^+ and K^+. Similar instillation studies were made in human subjects by Lindner, Cohen, Dreiling and Janowitz (1963) and Chapman, Werther and Janowitz (1967). They found that, following instillation of HCl into the stomach, there was a progressive diminution in concentration of H^+ in the instillate. Chapman's study included patients with pernicious anaemia and they suggest that back diffusion of H^+ was responsible for

the fall in its concentration, which was most marked in those patients, when compared with normal controls. Overholt and Polland (1968) confirmed these findings and showed not only a fall in H^+ but a gain in Na^+ in the instillate in patients with chronic gastritis. When the experiments were conducted during active gastric secretion stimulated by histamine, there did not appear to be a significantly greater absorption of H^+ from the gastric lumen of patients with hypochlorhydria when compared with normal controls. These findings suggest that, in the presence of gastric atrophy, more back diffusion occurs than in normal subjects, but that this is more important at low than at high rates of gastric secretion. Using a 'step test' technique with intravenous infusions of either histamine or pentagastrin, Aubrey, Kirkpatrick and Forrest (1968) have shown that the concentration of Na^+ is high and H^+ low in the gastric juice of patients with atrophic gastritis at low levels of gastric secretion, a finding compatible with increased back diffusion through a damaged mucosa. At maximal 'steady state' secretion, however, ionic relationships were similar in these patients to those found in duodenal ulcer patients and normal controls, confirming the views of Overholt and Polland, and indicating that maximal stimulation gives a valid estimate of acid output even when the mucosa is abnormal.

The finding in this study of a significantly lower mean acid concentration in those patients with atrophic mucosa on 'maximal' stimulation with intramuscular pentagastrin would seem to be in some measure at variance with the hypotheses and experimental findings outlined above. It is suggested that it may reflect a fallacy in the accuracy of estimations of 'peak' acid output as indices of maximal secretory capacity in the presence of atrophic gastritis in that the juice used for the estimation is not produced at 'steady state'

maximal secretion. It may have thereby lost hydrogen ions by back diffusion, thus reducing the H^+ concentration upon which the calculation of maximal output depends. However, assuming a constant volume of non-parietal secretion, a low H^+ concentration does indicate a reduction in the number of secreting parietal cells and by this token is an index of atrophic changes in the gastric mucosa.

Acid output and clinical diagnosis

It was not the purpose of this study to investigate the acid output in relation to discrete lesions of the stomach and duodenum, nor to evaluate the usefulness of the pentagastrin test in this connection, but to study the value of acid output estimation as a means of recognising atrophic gastritis. It is widely recognised that while mean figures for acid output vary significantly from one disease group to another (Table XXXVI), the range of output values obtained in any particular disease group is a wide one and overlap between the ranges in other groups is considerable (Kay, 1953 and 1967; Lawrie and Forrest, 1965; Abernethy, 1967; Johnston and Jepson, 1967). As a result of this overlap, little diagnostic value can be attached per se to the results of a test of acid secretion in an individual subject except where extreme values are found.

Christiansen (1968) has described an acid output, after maximal stimulation, of 10 mEq/hour as the 'gastritis threshold', outputs of less than this value indicating gastritis. Applying this criterion to the present study, and comparing the incidence of hypochlorhydria (acid output $<$ 10 mEq/hour) with the incidence of atrophic gastritis on biopsy, it will be seen (Fig. 18) that acid output estimation underestimated the incidence of gastritis in the duodenal and gastric ulcer patients but correlated closely with the incidence of gastritis in those with gastric cancer and non-ulcer dyspepsia.

	D.U.	G.U.	Ca.	Normal
Shearman, Finlayson and Wilson (1967) A.H.T.	33.0	14.0	5.0	19.0
Abernethy (1967) A.H.T.	42.0	12.0	10.0	24.0
Christiansen (1968) A.H.T.	41.0	14.0	-	24.0
Krenz (1968)	-	-	6.0	11.6
Johnston and Jepson (1967) Pentagastrin I.M.	43.0	24.0	6.0	27.0
Kirkpatrick, Lawrie, Forrest and Campbell (1969)				
Histamine I.V.	40.0	18.0	6.0	24.0
Pentagastrin I.M.	35.0	16.0	6.0	24.0
Present study	35.0	14.0	5.0	-

Table XXXVI: Mean acid output values, taken to the nearest whole number, in normal subjects and patients with peptic ulcer and gastric carcinoma in six published series, compared with the present study.

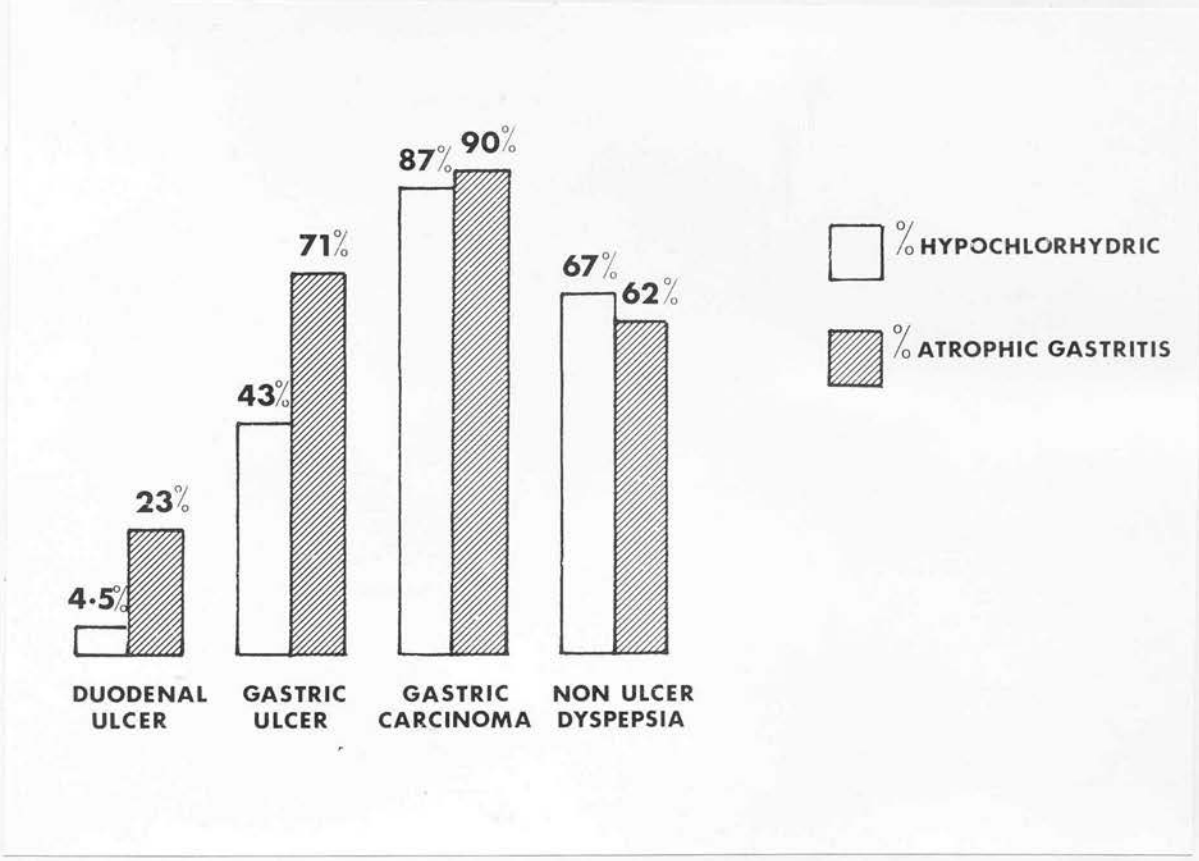


Figure 18: The incidence of hypochlorhydria compared with that of atrophic gastritis in the disease groups studied.

Hypochlorhydria is an unusual and contradictory finding in duodenal ulceration and is generally associated with the gastritis of pyloric stenosis, as was the case in the one subject in this study in whom it was found. The incidence of hypochlorhydria or achlorhydria with gastric carcinoma is high. Gilbertsen and Knatterud (1967) described 409 patients with this condition of whom 68.5 per cent were achlorhydric and a further 12% hypochlorhydric. Similar findings have been reported by many workers, including Statton and Horowitz (1955) who found an incidence of achlorhydria of 70-75% and hypochlorhydria of 10-15%, Shearman, Finlayson, Wilson and Samson (1966), 33% and 63%, and Kirkpatrick, Lawrie, Forrest and Campbell (1969), 42% and 38% respectively. Normal values are therefore not found in more than 20% at most of persons with gastric carcinoma. Ever since Von der Velden (1879) recorded the absence of free acid in the stomach of a patient with gastric cancer, argument has continued as to whether the reduction of acid output has been caused by the cancer itself, or by other causes. Undoubtedly, where there is extensive infiltration by carcinoma of the secretory mucosa of the body of the stomach, acid production will be impaired but in most instances reduced acid output is probably the result of atrophic gastritis. As has already been discussed, the incidence and extensiveness of atrophic gastritis is high in carcinoma of the stomach, and the gastritis precedes the onset of malignant change. In a group of patients studied at the Mayo Clinic, Comfort, Kelsey and Berkson (1947) found that 46% were achlorhydric 2 years prior to the development of cancer, and 68% were achlorhydric at the time of diagnosis.

Of 44 patients in this study with gastric ulcer (21 benign and 23 malignant), hypochlorhydria was found in 29. Of these, 20 (69%) ulcers were malignant and 9 benign. Of the 15 patients in whom

normal or high values of acid output were found, there were 12 benign, and 3 (20%) malignant ulcers. Thus, while normal or high values do not exclude carcinoma, and low values are not diagnostic of carcinoma, hypochlorhydria suggests the probability that an ulcer is likely to prove malignant, by virtue of its associated atrophic gastritis.

Conclusion

Of 111 patients, 40 with non-atrophic mucosa and 71 with atrophic gastritis, hypochlorhydria was found in 62. Of these, 56 (90%) had atrophic gastritis. A H^+ concentration of less than 100 mEq/litre on maximal stimulation was found in 77 of the subjects of whom 65 (84%) had atrophic gastritis. Normal or high values of acid output were found in 49 patients and of these 70% had normal mucosa, but 30% had atrophic gastritis. An acid concentration of 100 mEq/litre or more was found in 34 patients of whom 28 (82%) had normal mucosa.

From a study of Table XXXVII it will be seen that both parameters, i.e. maximal acid output, and H^+ concentration, are of importance in the recognition of atrophic gastritis. Hypochlorhydria or a low acid concentration reflect the histological appearance of the gastric mucosa with a high degree of accuracy. The finding of normal or high levels of output, however, was less reliable in excluding the existence of atrophic gastritis, but the study of acid concentration levels in these cases significantly reduced the number of instances where acid output figures would otherwise have given misleading information.

	Non-atrophic mucosa	Atrophic mucosa
Acid output $<$10 mEq/hour	6 (10%)	56 (90%)
Acid output $>$10 mEq/hour	34 (69%)	15 (31%)
H^+ concentration $<$100 mEq/l	12 (16%)	65 (84%)
H^+ concentration $>$100 mEq/l	28 (82%)	6 (18%)

Table XXXVII: A comparison of acid output, and acid concentration as indices of the presence or absence of atrophic gastritis.

CHAPTER 7

RADIOLOGICAL EXAMINATION

1. Introduction

With the advent of methods for gastric mucosal biopsy, it has become possible to compare the histological appearances of the gastric mucosa with the findings of other diagnostic methods. Prior to this, the radiological diagnosis of diffuse lesions of the stomach had received little attention, and the radiological diagnosis of 'gastritis' was usually based upon the finding of thickened rugae or enlarged folds, findings which had no pathological basis. Joske, Finckh and Wood (1955) found no correlation between gastric biopsy findings, and the appearances of the gastric mucosa on barium meal, and Schinz, Baensch, Friedl and Uehlinger (1954) and Glass (1957) were of the opinion that radiology had little to offer in the diagnosis of gastric atrophy. Subsequently, however, Badenoch, Kemp and Richards (1956) by a study of the size of the gastric rugae on barium meal examination, were able to make a diagnosis of gastric atrophy in 20 of 25 patients with pernicious anaemia. Their findings have been subsequently supported by other workers, and criteria for the radiological diagnosis of gastric atrophy have been established.

These criteria consist of (a) a stomach of tubular shape, and (b) of small volume; (c) a smooth or 'bald' appearance of the gastric fundus (d) the presence of fine 'tissue paper' mucosal folds in the body and fundus (e) absence or diminution in the size of rugal folds along the greater curvature (Laws and Pitman, 1960), and (f) a reduction in the size of mucosal folds along the greater curvature of less than 0.5 cm (Bock, Kemp and Richards, 1963) (Fig. 19). Employing these criteria, these workers, and others (Joske and Vaughan, 1962; James, Melrose, Davidson and Russell, 1965) have shown a substantial correlation between the presence of severe atrophic mucosal changes and the presence of radiological signs of gastric atrophy, especially

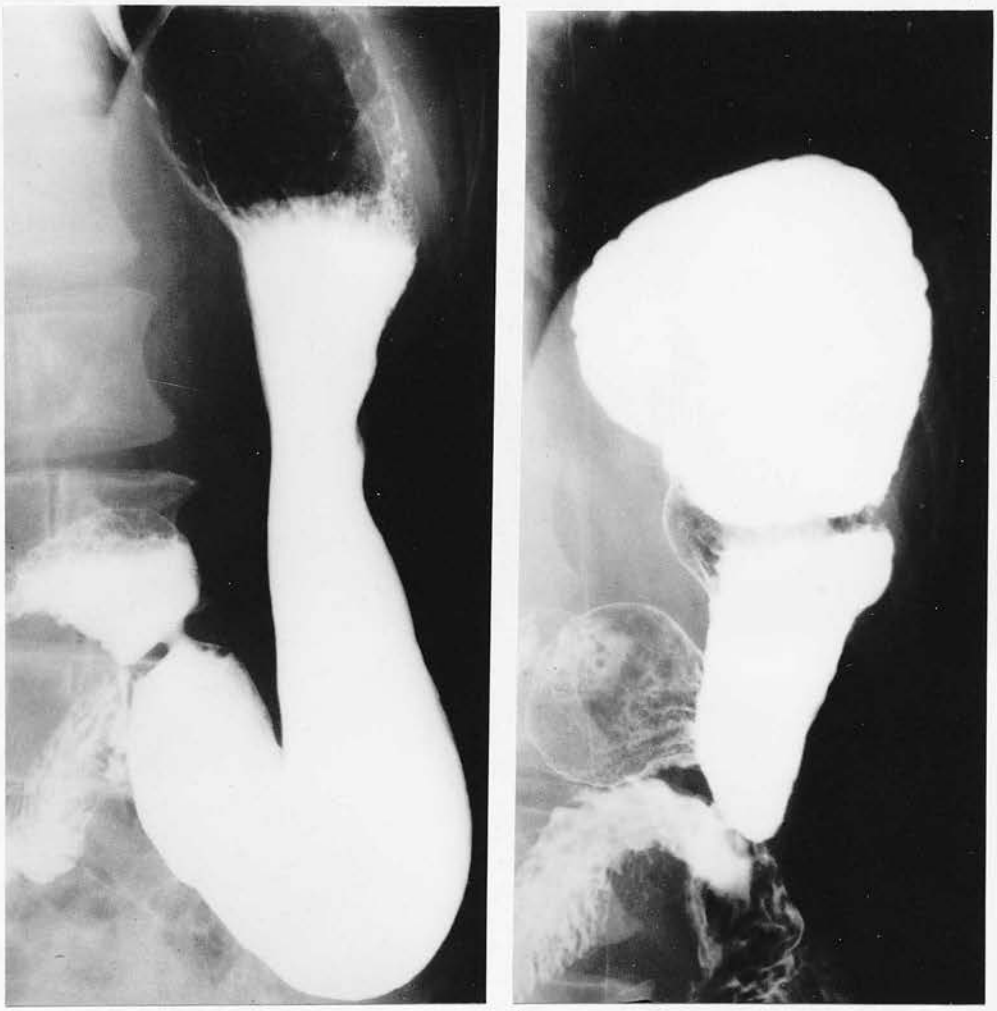


Figure 19: Barium meal radiographs (a) in the erect position, and (b) supine, showing a 'bald' gastric fundus and absence of mucosal folds in a characteristically small volume tubular stomach.

in the absence of focal changes in the stomach. Despite these studies, the radiological diagnosis of gastric atrophy is viewed by the majority of clinicians and radiologists with some disparagement and scepticism.

2. Material and methods

Each patient in the study was subjected to barium meal examination as part of the investigation of his dyspepsia. At the time that the examination was requested, no particular stress was laid upon the question of the presence or otherwise of atrophic change, but clinical notes were available to the radiologist. The barium meal examinations were conducted by standard methods using an image intensifier in most cases. Erect and supine films were taken both with the mucosa coated with barium and with the stomach filled with barium. The examinations were carried out, and the films reported on, by a number of different radiologists on the staff of the Department of Diagnostic Radiology in the United Cardiff Hospitals. The films of 88 of the patients were subsequently reviewed independently by two radiologists who were unaware at the time of this review of the histological findings of the gastric mucosa, or of any other clinical or pathological parameters relating to the patients.

In assessing the accuracy of the radiological diagnosis of gastric atrophy in the initial reporting of the barium meal examinations, the fact that atrophy was reported was taken as being indicative of radiological gastric atrophy (R.G.A.), while no mention of it in the report assumed its absence. In the subsequent review of the films, five criteria of R.G.A. were each specifically sought: (i) mucosal folds of < 0.5 cm (ii) tubular shape of stomach (iii) small volume stomach (iv) 'bald' gastric fundus, and (v) tissue paper folds. A score was given for each, and the presence of two or more criteria was taken as being indicative of the presence of gastric atrophy.

The results of the initial, and subsequent retrospective radiological assessments, were compared with the gastric mucosal biopsy findings, and with the gastric acid output in each case. The correlation between the radiological assessment, and the findings on gastroscopy and gastric photography, will be discussed in subsequent chapters.

3. Results

A. Initial assessment

(a) Comparison of radiological and gastric biopsy findings

Of 71 patients with histological evidence on biopsy of atrophic gastritis, R.G.A. was recognised and reported in 13 (19%). Of 40 with normal mucosa, R.G.A. was reported in 3 (7.5%) (Table XXXVIII). It will be noted from a study of this table, however, that of those with atrophic change, R.G.A. was reported in 12 (35%) of 34 patients with no focal lesion in the stomach and in only 1 (2.7%) of those with focal gastric lesions. A similar trend is seen in the false positive diagnosis of R.G.A. in those with normal mucosa, 2 (13%) of 15 cases with no focal lesion being so diagnosed compared with 1 (4%) of 25 patients with focal lesions.

The finding of R.G.A. was compared with the grade of the histological appearances of the mucosa in the group as a whole, and in those with no focal lesion in the stomach (Table XILa and b). The accuracy of recognition was assessed for each grade and it will be seen from a study of these tables that in the group as a whole severe atrophic gastritis and gastric atrophy were more often correctly recognised radiologically than mild or moderate atrophic gastritis. Excluding those with focal gastric lesions, moderately severe gastritis was still recognised radiologically less often than the severer grades of the condition, but in 3 of the 4 cases with mild atrophic gastritis,

Mucosal histology	Radiological assessment	D.U.	G.U.	Gastric cancer	Non-ulcer dyspepsia	P.A.	Total
Atrophic	Atrophic	0	1	0	9	3	13 (19%)
	Non-atrophic	5	14	17	16	6	58 (81%)
Non-atrophic	Atrophic	0	1	0	2	0	3 (7.5%)
	Non-atrophic	17	5	2	13	0	37 (92.5%)

Table XXXVIII: The initial radiological assessment of the presence or absence of gastric atrophy in patients with, and without, histological evidence of atrophic gastritis.

Radiological diagnosis	Non-atrophic mucosa		Atrophic mucosa				Total
	Normal mucosa	Superficial gastritis	Atrophic gastritis Mild	Mod.	Severe	Gastric atrophy	
Atrophic	3	0	3	2	6	1	15
Non-atrophic	29	8	11	25	20	3	96
Total	32	8	14	27	26	4	111
% correct	90	100	21	8	30	25	44
Accuracy %	92.5				17		

Table XILa: The initial radiological assessment on barium meal examination of the presence or absence of R.G.A. compared with the histological grade of the gastric mucosa in the whole group under study.

Radiological diagnosis	Non-atrophic mucosa		Atrophic mucosa				Total
	Normal mucosa	Superficial gastritis	Atrophic gastritis Mild	Mod.	Severe	Gastric atrophy	
Atrophic	2	0	3	2	6	1	14
Non-atrophic	9	4	1	6	12	3	35
Total	11	4	4	8	18	4	49
% correct	82	100	75	25	33	25	51
Accuracy %	87				35		

Table XILb: The initial radiological assessment on barium meal examination of the presence or absence of R.G.A. compared with the histological grade of the gastric mucosa in those patients without focal gastric lesions.

this was recognised radiologically. No patient exhibiting superficial gastritis was reported upon as showing signs of R.G.A. and normal mucosa was correctly recognised radiologically in 90% of the group as a whole and in 82% of those without focal lesions, reflecting a false positive diagnosis of R.G.A. in 10% and 18% of the two groups respectively.

(b) Comparison of radiological findings and gastric acid output

The mean maximal acid output after intramuscular pentagastrin in a dose of 6 ug/kg of the 16 patients in whom R.G.A. was found, was 5.5 mEq per hour. That of the 95 patients whose gastric mucosa appeared normal to radiological examination was 15.4 mEq per hour. These means were compared using Student's 't' test, and were found to differ significantly ($p < 0.01$) (Table XL).

The acid output of the 13 patients in whom biopsy and radiological findings were found to agree, was less than 10 mEq/hour in each case, while of the 3 cases with R.G.A. but non-atrophic mucosa, hypochlorhydria was present in one, and normal acid levels in the other two. Of the 95 patients in whom R.G.A. was not reported, 58 had histological evidence of atrophic gastritis, and 51 were hypochlorhydric (Table XLI).

B. Retrospective assessment

(a) Radiological signs of gastric atrophy

As has already been stated, the diagnosis of gastric atrophy was reached if two or more of the radiological criteria were present in the barium meal films. The frequency with which these criteria were found is shown in Figure 20, and it will be seen that the most reliable signs were the 'bald' gastric fundus, mucosal folds or rugae of less than 0.5 cm, and the finding of a tubular shaped stomach. 'Tissue paper' folds and a small volume stomach were uncommon findings.

Radiological assessment	No.	Mean acid output (mEq/hour)
Atrophic	16	5.5
Non-atrophic	95	15.4

Table XL: The mean acid output of those patients with and without R.G.A. on initial assessment ($p < 0.01$).

Radiological assessment	No.	Mucosa		Acid output	
		Atrophic	Non-atrophic	Hypochlorhydria	Normal values
Atrophic	16	13	3	14	2
Non-atrophic	95	58	37	51	44

Table XLI: The initial radiological assessment compared with gastric mucosal histology and maximal acid output.

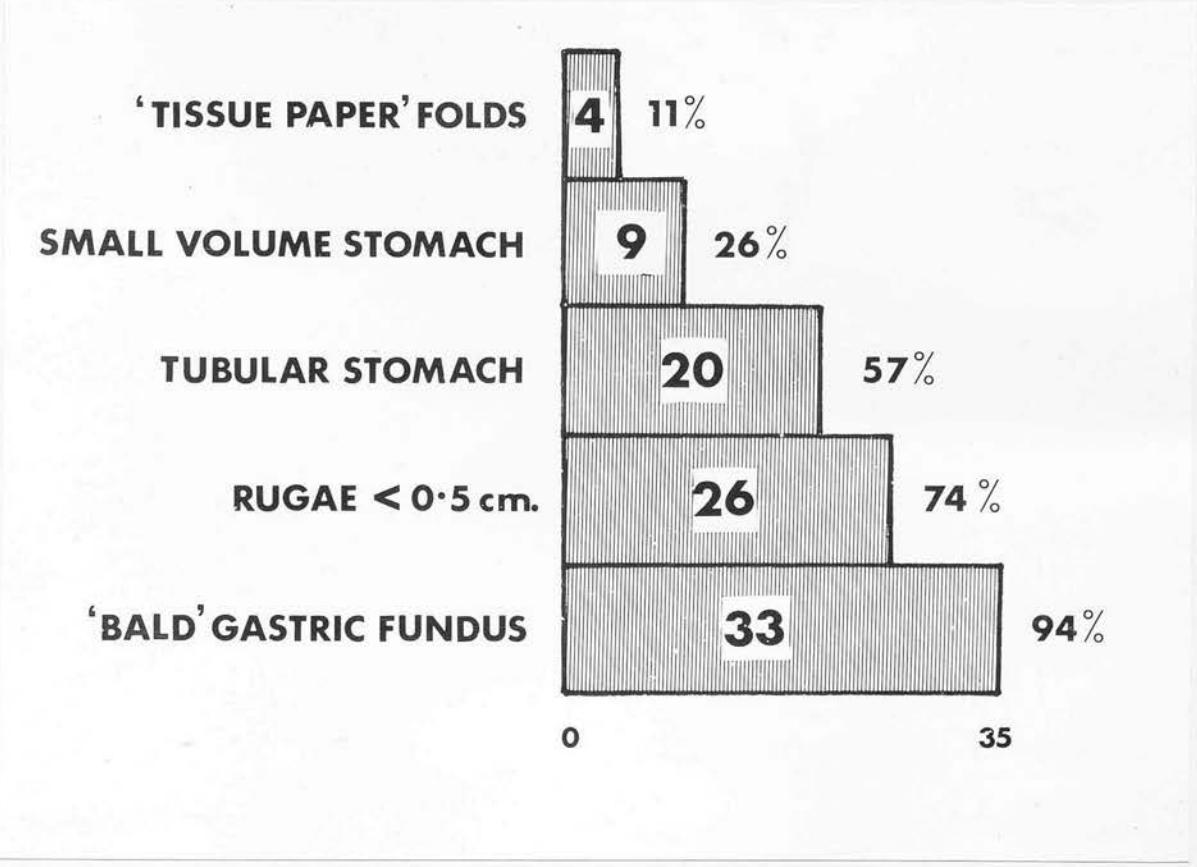


Figure 20: The frequency with which the signs of radiological gastric atrophy were found in 35 subjects.

(b) Comparison of radiological and gastric biopsy findings

Of 55 patients with histological evidence of atrophic gastritis, R.G.A. was deemed to be present in 31 (56%) by the criteria described above. Of 33 patients with non-atrophic mucosa, R.G.A. was present in 4, a false positive incidence of 12% (Table XLII). When those patients in whom barium meal had not revealed a focal lesion were studied separately, R.G.A. was recognised in 19 (70%) of 27 patients with atrophic gastritis and in 2 (16%) of 12 patients with non-atrophic mucosa. On the other hand, radiological signs of gastric atrophy were found in 12 (42.5%) of 27 patients with atrophic gastritis accompanying a focal lesion, and in 2 (9.5%) of those patients with normal gastric mucosa.

The presence of R.G.A. was compared with the grade of the histological appearance of the gastric mucosa in the group as a whole and in those without a focal lesion (Table XLIIIa and b) and it will be seen that it increased in frequency with the severity of atrophic change in both groups of patients. It was present in 75% of those patients with severe atrophic gastritis, and in both cases of gastric atrophy included in the study (in 14 - 77% - of 18 cases with severe atrophic change), this incidence being irrespective of the presence or otherwise of a focal lesion. In the less severe grades of atrophic gastritis, however, the incidence was lowest when mild atrophic gastritis accompanied a focal lesion, and highest in moderate atrophic gastritis in a stomach free of other radiological features. Four false positives were found in the whole group of 33 patients with normal mucosa, 2 in patients with focal lesions (1 benign gastric ulcer and 1 carcinoma) and in two cases with non-ulcer dyspepsia. The overall agreement between biopsy and radiology irrespective of diagnosis was 68% (Table XLIV).

Mucosal histology	No.	Radiological assessment	Duodenal ulcer	Gastric ulcer	Gastric cancer	Non-ulcer dyspepsia	Pernicious anaemia	Total
Atrophic	55	Atrophic	1	3	8	13	6	31 (57%)
		Non-atrophic	4	9	3	8	0	24 (43%)
Non-atrophic	33	Atrophic	0	1	1	2	0	4 (12.0%)
		Non-atrophic	17	2	0	10	0	29 (88%)
Total	88		22	15	12	33	6	88

Table XLII: The retrospective radiological assessment of the presence or absence of gastric atrophy in patients with or without histological evidence of atrophic gastritis.

Radiological assessment	Non-atrophic mucosa		Atrophic mucosa				Total
	Normal mucosa	Superficial gastritis	Atrophic gastritis Mild	Mod.	Severe	Gastric atrophy	
Atrophic	3	1	4	9	16	2	35
Non-atrophic	23	6	7	12	5	0	53
Total	26	7	11	21	21	2	88
% correct	88	86	36	43	75	100	68
Accuracy %	88				55		

Table XLIIIa: The retrospective radiological assessment on barium meal examination, of the presence or absence of R.G.A. compared with the histological grade of the gastric mucosa in all 88 patients studied.

Radiological assessment	Non-atrophic mucosa		Atrophic mucosa				Total
	Normal mucosa	Superficial gastritis	Atrophic gastritis Mild	Mod.	Severe	Gastric atrophy	
Atrophic	2	0	2	3	12	2	21
Non-atrophic	8	2	2	2	4	0	18
Total	10	2	4	5	16	2	39
% correct	80	100	50	60	75	100	74
Accuracy %	84				70		

Table XLIIIb: The retrospective radiological assessment on barium meal examination, of the presence or absence of R.G.A. compared with the histological grade of the gastric mucosa in 39 patients without focal gastric lesions.

Radiological assessment	Biopsy		Total	% agreement
	Atrophic	Not atrophic		
Atrophic	31	4	35	89
Not atrophic	24	29	53	45
Total	55	33	88	
% agreement	56	88		68

Table XLIV: The overall degree of agreement between gastric biopsy findings and radiological assessment of the gastric mucosa.

(c) Comparison of radiological findings and acid output

The mean maximal acid output of those with R.G.A. was 3.1 mEq/hour compared with a mean of 24.6 mEq/hour in those with no such radiological signs. This difference was highly significant ($p < 0.001$; Table XLV). Hypochlorhydria was present in 33 (94%) of the 35 patients with R.G.A. Of the four patients of this number in whom normal gastric mucosa was found, two were hypochlorhydric and two had normal levels of acid output. In the 53 patients in whom the features of R.G.A. were not present, hypochlorhydria was present in 13 and atrophic mucosa in 24 (Table XLVI). Of these 24 patients with histological atrophic gastritis, 12 had hypochlorhydria, and the remaining 12 had levels of acid output in excess of 10 mEq/hour. In these latter cases, therefore, neither radiological signs nor acid output levels suggested the presence of atrophic gastritis. None of these patients had severe atrophic gastritis, 5 having mild changes and 7 moderate. A further single patient had hypochlorhydria but no radiological signs of gastric atrophy, and a normal gastric biopsy. The overall agreement between acid output, as an index of the presence or absence of atrophic gastritis, and the radiological assessment was 83%, irrespective of clinical diagnosis (Table XLVII).

Discussion

From the analysis of these results certain conclusions can be drawn. Firstly, if gastric atrophy is specifically sought employing the accepted criteria for its radiological diagnosis, it is recognisable in its severer forms with an acceptable degree of accuracy of some 77%. Lesser degrees of atrophic change are less readily recognised. The explanation for this probably lies in the fact that the radiological signs probably owe their origin to changes in the muscle coat of the organ. The gastric atrophy of pernicious anaemia is not only an

Radiological assessment	No.	Mean acid output (mEq/hour)
Atrophic	35	3.1
Non-atrophic	53	24.6

Table XLV: The mean acid output of those patients with and without R.G.A. on retrospective assessment ($p < 0.001$).

Radiological assessment	No.	Mucosa		Acid output	
		Atrophic	Non-atrophic	Hypochlor-hydria	Normal values
Atrophic	35	31	4	33	2
Non-atrophic	53	24	29	13	40

Table XLVI: The retrospective radiological assessment compared with gastric mucosal histology, and maximal acid output.

Radiological assessment	Acid output		Total	% agreement
	Atrophic	Non-atrophic		
Atrophic	33	2	35	94
Non-atrophic	13	40	53	75
Total	46	42	88	
% agreement	72	95		83

Table XLVII: The overall degree of agreement between acid output (10 mEq/hour or less as the index of atrophic gastritis) and the radiological assessment of the gastric mucosa.

atrophy of the mucosa of the gastric body, but of the muscle coat as well (Magnus, 1958) and it is now generally recognised that this condition is the end result of a progressive atrophic gastritis (Markson, 1955). Muscular atrophy therefore is likely to be a feature seen with increasing frequency in keeping with the severity of the atrophic gastritis, in which atrophy and fragmentation of the muscularis mucosae is a universal finding. When it is recollected that the mucosal pattern as seen by the radiologist is a 'relief' pattern caused by raised mucosal folds, their absence or diminution in size is probably simply a reflection of this muscular atrophy. The increasing accuracy of diagnosis of gastric atrophy with increasing severity of the condition histologically in this study is in keeping with the very similar findings of Joske and Vaughan (1962) and with those of James, Nelson, Davidson and Russell (1965) who found R.G.A. in 11 of 12 cases with histologically proven gastric atrophy as opposed to 4 out of 16 cases with atrophic gastritis of unstated but varying severity. The correlation between low gastric acid output and the finding of R.G.A. lends support to the radiological signs being associated with a diffuse atrophic gastritis involving the whole of the body mucosa. Fifty per cent of those cases with the histological changes of atrophic gastritis on biopsy but with no signs of R.G.A., had acid output levels in the normal range. Over half of these patients had histological atrophic gastritis of moderate severity in which, were the changes diffuse, muscular atrophy would be expected. It is possible that a normal barium meal may therefore not only indicate the absence of severe changes but may also be indicative of a patchy rather than a diffuse atrophic gastritis.

Secondly, it is clear from these findings and from similar findings by Joske and Vaughan (1962) that the presence of a focal

gastric or duodenal lesion renders the finding of R.G.A. less likely than in a stomach otherwise free of pathological changes. The reason for this is not entirely clear, as with a few exceptions, there was no gross infiltration of the stomach by carcinoma in the cases studied. It may be, however, that the muscular irritability and distortion of the stomach associated with ulceration plays a part, as may the excess of mucus often associated with gastric cancer or benign ulceration.

Thirdly, the findings of a 'bald' gastric fundus and of gastric rugae of less than 0.5 cm were the most constant and reliable radiological signs of gastric atrophy, those of a small volume stomach and of 'tissue paper' folds being infrequently noted. These findings are similar to those of Laws and Pitman who found that the finding of small or absent rugae was the commonest sign and that the other signs were less frequently seen (Table XLVIII).

In conclusion, it may be said (a) that the finding of radiological gastric atrophy is highly likely to indicate the presence of atrophic gastritis (false positive incidence 12%) (b) that the accuracy of radiological recognition of severe grades of atrophic gastritis is clinically acceptable at 77% (c) that failure to recognise atrophic gastritis, if present, is likely to be due to either a mild degree of gastritis or a patchy distribution of the lesion in the gastric mucosa (d) the presence of a focal gastric lesion renders radiological recognition of atrophic gastritis more difficult, especially in less severe grades of the condition.

Author	Cases of R.G.A. No.	Bald fundus	Small rugae	Tubular stomach	Tissue paper folds
Laws and Pitman (1960)	71	70%	80%	69%	32%
Present study	35	94%	74%	57%	11%

Table XLVIII: The frequency of four criteria in the diagnosis of radiological gastric atrophy in the present study, compared with Laws and Pitman (1960).

CHAPTER 8

GASTROSCOPY

Introduction

The history of gastroscopy has been reviewed by Schindler (1950) and more recently by Nelson (1970) and may be said to date back to 1868 when Kussmaul attempted to visualise the interior of the stomach of a sword swallower using a 13 mm diameter hollow tube. Not only did his attempt stimulate scientific endeavour into the development of practical instruments for gastroscopy, but, as Gibbs (1967) has pointed out, he showed for the first time that the teeth, oesophagus, and stomach, could be safely aligned for the passage of a rigid examining instrument. The era of gastroscopy, using rigid gastroscopes, lasted until 1932 (Jackson, 1907; Schindler, 1923; Henning, 1931; Moutier, 1932) when the Wolf-Schindler flexible gastroscope was introduced. This instrument had a flexible distal section consisting of jointed cylinders, each containing a lens, thus allowing safer and easier gastroscopy while brining a greatly increased area of the gastric mucosa within the view of the gastroscopist (Schindler, 1933). One of the defects of this instrument lay in the inability to control the flexible portion and this was overcome in several models by the use of a pull-wire operated from the proximal end of the instrument. Such an instrument, the Hermon Taylor Gastroscope, was widely used in this country until the introduction of fiberoptics in 1958.

In 1958, Hirschowitz, Curtis, Peters and Pollard, first described a gastroscope whose optical system depended upon the principle of fiberoptics. It has been known since 1870 that light could be trapped by a conductor, and by multiple internal reflection, be made to follow the curve of the conductor, provided that it is suitably coated (Goldman, Bereskin and Shackney, 1960). A narrow glass rod or fibre will act in this way, and by individually coating each member of a

bundle of glass fibres, an image may be transmitted by such a bundle with little loss of light intensity and with a highly resolved definition irrespective of the degree of flexion which may be applied to it (Fig. 21). The advantage of employing this principle in gastroscopy lies in the ease and safety with which the flexible instrument may be passed, and the greatly increased scope for visualisation of all parts of the stomach. This latter feature is especially relevant in the more recently introduced fiber-optic gastroscopes in which a controllable distal segment is incorporated. Employing this, not only is it possible to adequately visualise the body and pyloric antrum, but the flexible tip can be doubled back upon itself in order to examine the fundus and cardia, areas hitherto immune to gastroscopic examination.

Schindler (1950) defined three types of gastritis which were recognisable by gastroscopy, namely catarrhal, hypertrophic and atrophic gastritis, and in his monograph described these clinical entities in detail. Unfortunately, these descriptions had no histological foundation and thus it was not until the advent of suction biopsy that accurate correlation between gastroscopic findings and the state of the gastric mucosa could be investigated. Gastroscopically, atrophic gastritis is seen as a mucosa which is pale, often with a bluish tinge, has a thin appearance with visible blood vessels and an absence or diminution of the mucosal folds or rugae (Jones, Benedict and Dempton, 1935; Palmer, 1949; Atkins and Benedict, 1956). A number of reports have been published describing the correlation between biopsy findings and the appearances on gastroscopy. Joske, Finckh and Wood (1955) found little correlation between gastroscopic findings and gastric biopsy in 258 instances and concluded that the value of gastroscopy lay in the detection of focal,

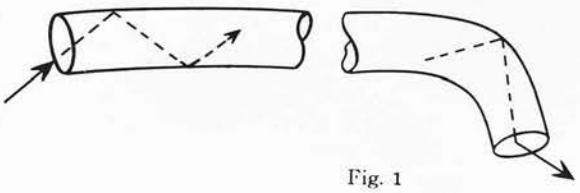


Fig. 1

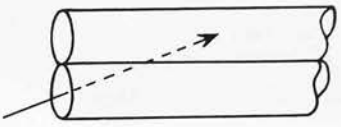


Fig. 2

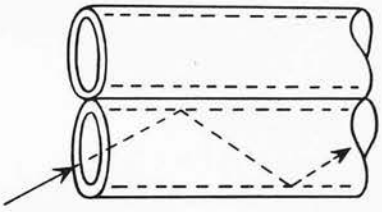


Fig. 3

Figure 21: Diagram showing (1) how light passes along a curved tube by multiple internal reflection, and (2) and (3) that by coating individual fibres of a bundle, each transmits an image individually by this means.

rather than diffuse, gastric lesions. This view was also shared by Maratka and Setka (1961) from their experience of 120 cases in whom both examinations were carried out, and by Atkins and Benedict (1956) and Hardt, Schwartz and Steigmann (1948). On the other hand, Palmer (1950) and Brühl and Krentz (1970) found a high degree of correlation between biopsy findings and gastroscopic appearances, especially when the gastroscopic appearances suggested gastritis. However, of 98 normal gastroscopies in Brühl and Krentz's series, only 38 had normal mucosa on biopsy.

It would thus seem that most workers in this field have not shown that gastroscopy is a reliable method of recognising diffuse gastric lesions, and that the finding of a normal appearance of the gastric mucosa by no means excludes the possibility of gastritis being present.

Material and methods

Gastroscopy was performed upon 54 of the 111 patients in this study from whom gastric biopsies had been obtained. The examination was carried out by one of three surgeons, the author, Professor A. P. M. Forrest and Professor R. Shields. The assessment of the state of the gastric mucosa was made with no knowledge at the time of the examination of the histological appearances of the gastric biopsy. One of three instruments was used, Hermon Taylor semi-rigid gastroscope, Hirschowitz fiberscope or Olympus G.T.F. fiberscope. The examination was carried out in the conscious patient with premedication with an opiate and atropine, the fauces and pharynx being anaesthetised with a topical application of lignocaine.

Results

(a) Comparison of gastroscopic findings and gastric mucosal histology

Gastroscopy was performed upon 35 patients with histologically

proved atrophic gastritis and 19 with non-atrophic gastric mucosa. Atrophic gastritis was recognised in 19 (54%) of those with histological evidence of the condition, and in 3 of those with non-atrophic mucosa, giving a false positive incidence of 14% (Table XLIX). When the gastroscopic diagnosis of atrophic gastritis was compared with the histological grade of the gastric mucosa, it will be seen (Table L) that 84% of those with histologically normal mucosa and 83% of those with severe atrophic change were correctly recognised. With less severe grades of atrophic gastritis, accuracy fell to 57% for those with mild changes and to 31% of those with moderate changes. Overall, the gastroscopic and biopsy findings agreed in 65% of cases. The 27 patients without focal gastric or duodenal lesions were analysed separately, and from a study of Table LI it will be seen that the overall correlation remained unchanged. A higher percentage of cases with atrophic gastritis were correctly recognised gastroscopically (62.5%) especially those with mild and severe changes, but all three false positives occurred in this group, thus increasing the false positive incidence to 27% of patients with non-atrophic mucosa on biopsy.

(b) Comparison of gastroscopic assessment with maximal acid output

The mean maximal acid output of those patients in whom atrophic gastritis was diagnosed on gastroscopy was 6.2 mEq/hour compared with 18.4 mEq/hour in those with gastroscopically normal mucosa. These means were compared using Student's 't' test and found to differ significantly ($p < 0.01$) (Table LII). Hypochlorhydria was present in 18 (82%) of the 22 patients in whom atrophic gastritis was seen gastroscopically, and normal values of acid output were found in 22 (69%) of 32 patients whose mucosa appeared normal (Table LIII). Thus, overall agreement between acid output and the gastroscopic appearance of the mucosa was found in 40 (74%) of the cases. As was found in the

Gastroscopic assessment	Biopsy		Total	% agreement
	Atrophic	Non-atrophic		
Atrophic	19	3	22	86
Non-atrophic	16	16	32	50
Total	35	19	54	
% agreement	54	84		65

Table XLIX: The degree of agreement between the findings on gastric biopsy and gastroscopy.

Gastroscopic assessment	Non-atrophic mucosa		Atrophic mucosa			Total
	Normal mucosa	Superficial gastritis	Atrophic gastritis Mild	Mod.	Severe	
Atrophic	3	0	4	5	10	22
Non-atrophic	12	4	3	11	2	32
Total	15	4	7	16	12	54
% agreement	80	100	57	31	83	65
Accuracy %	84		54			

Table L: The gastroscopic assessment of the presence or absence of atrophic gastritis in 35 patients with histologically proven atrophic gastritis and 19 with non-atrophic mucosa.

Gastroscopic assessment	Non-atrophic mucosa		Atrophic mucosa			Total
	Normal mucosa	Superficial gastritis	Atrophic gastritis Mild	Mod.	Severe	
Atrophic	3	0	3	1	6	13
Non-atrophic	5	3	1	4	1	14
Total	8	3	4	5	7	27
% correct	62.5	100	75	20	86	67
Accuracy %	73		62.5			

Table LI: The presence or absence of atrophic gastritis as judged by gastroscopy, compared with the histological grade of the gastric mucosa in those patients without focal gastric or duodenal lesions.

Gastroscopic assessment	No.	Mean acid output (mEq/hour)
Atrophic	35	6.2
Non-atrophic	19	18.4

Table LII: The mean acid output in those patients with, and without, atrophic gastritis on gastroscopy ($p < 0.01$).

Gastroscopic assessment	Maximal acid output		Total	% agreement
	Atrophic	Non-atrophic		
Atrophic	18	4	22	82
Non-atrophic	10	22	32	69
Total	28	26	54	
% agreement	64	85		74

Table LIII: The degree of agreement between maximal acid output (10 mEq/hour HCl or less being taken as the index of atrophic gastritis) and the findings on gastroscopy.

case of barium meal examination, a group of patients was found in whom neither acid output nor gastroscopy correlated with the gastric biopsy. In this group there were 6 such cases, 4 cases with gastric ulceration, three with moderate and one with mild atrophic gastritis, with normal acid output levels and normal mucosa on gastroscopy, and 2 with normal mucosa on biopsy, but hypochlorhydria and gastroscopic signs of atrophic gastritis.

(c) Comparison of gastroscopic and radiological assessments

Of the 54 patients in whom gastroscopy was performed, the barium meal films were available for scrutiny as to the presence of radiological gastric atrophy as described in the previous chapter, in 47. The respective assessments were compared (Table LIV) and it will be seen that of 21 patients with gastroscopic signs of atrophic gastritis, R.G.A. was present in 13 (62%). Of 26 patients with no signs of atrophic gastritis on gastroscopy, R.G.A. was found in 4, the mucosa being radiologically normal in the remaining 22 (85%). Overall agreement between the findings by the two methods was found in 76%.

Discussion

Although an overall agreement of 65% was found between the gastroscopic assessment of the normality or otherwise of the gastric mucosa and the gastric biopsy findings, only 54% of those cases with atrophic gastritis were recognised by gastroscopy. On the other hand, 86% of those so diagnosed gastroscopically had atrophic gastritis on biopsy. These findings have been compared with the findings of other published series (Joske, Finckh and Wood, 1955; Atkins and Benedict, 1956; Brühl and Krentz, 1970) whose results with regard to the gastroscopic recognition of atrophic gastritis have been extrapolated from their data (Table LV). It will be seen that in these series the

Gastroscopic assessment	Radiology		Total	% agreement
	Atrophic	Non-atrophic		
Atrophic	13	8	21	62
Non-atrophic	4	22	26	85
Total	17	30	47	
% agreement	76	73		76

Table LIV: The agreement between radiology and gastroscopy as to the presence or absence of atrophic gastritis.

	No. studied	Histological atrophic gastritis	Gastroscopic atrophic gastritis
		% correlation with gastroscopy	% correlation with biopsy
Joske, Finckh and Wood, 1955	207	40	60
Atkins and Benedict, 1956	188	33	42
" Bruhl and Krentz, 1970	253	43	79
Present study	54	54	86

Table LV: The accuracy of recognition of atrophic gastritis by gastroscopy in 3 published series compared with the present study.

accuracy of recognition lay between 33 and 54%, though when atrophic gastritis was considered to be present, its existence was confirmed by biopsy in the majority of cases.

A number of reasons may be advanced to account for this poor correlation between gastroscopic findings and the presence of atrophic change in the gastric mucosa. The more severe the atrophic change, the greater is the likelihood of gastroscopic diagnosis, and this may be accounted for, as in radiological diagnosis, by increasing muscular atrophy in these cases, as has already been discussed. A further factor is the thinness of the gastric mucosa in severe atrophy in contrast with the maintenance of mucosal thickness by inflammatory infiltrate seen in less severe grades of the condition in which the classical gastroscopic signs of atrophic gastritis are unlikely to be apparent. In addition to these factors must be added the physical variations within the stomach during the examination. There is no means of standardising the degree of inflation of the stomach during the examination, and thus the degree of stretching of the gastric wall varies from subject to subject with corresponding variation in the degree of vascularity of the mucosa and flattening of mucosal folds. Added to this, the distance of the lens and light of the gastroscope from the mucosa is a further variable, resulting in inconstant intensity of illumination.

In conclusion, therefore, it may be said that gastroscopy has not been shown to be a reliable method of recognising atrophic gastritis and that the finding of an apparently normal mucosa in no way excludes the existence of the condition. The gastroscopic diagnosis of atrophic gastritis is, however, likely to be correct when it is made, and should be an indication for further confirmatory investigation.

CHAPTER 9

GASTRIC PHOTOGRAPHY

The earliest attempt to photograph the interior of the stomach was made before radiology had been successfully applied to the gastrointestinal tract. Recognisable black and white photographs of the stomach were obtained by Lange and Meltzing (1898) employing a camera attached to a flexible tube which was swallowed by the patient. Success did not, however, follow the development of this original instrument. Further exploration of the possibilities of 'blind' intragastric photography was conducted by Heilpern and Porges (1930) who devised an instrument, the 'gastrophotor', which was a camera with five pinhole apertures arranged in a circle and designed to take panoramic photographs of the gastric lumen. Although black and white photographs of good quality were obtained with this instrument (Berney, 1931) it never achieved popularity, perhaps largely due to the success of Henning (1937) who had pioneered the technique of direct photography as an adjunct to gastroscopy. Employing the principle of attaching a camera to the proximal end of a gastroscope he was able to record his gastroscopic findings in the form of black and white photographs, which he subsequently painted in water-colour. With the ready availability of colour film in the post-war years, high quality gastric photographs were obtained using an internal electronic flash synchronised with a flexible gastroscope (Debrey and Housset, 1948). This method of gastric photography continues to be successfully used in association with modern fiberoptic gastroscopes in which the incorporation of biopsy instruments precludes the inclusion of an intragastric camera (Gwyn Williams, Truelove, Gear, Monarella and Fitzgerald, 1968).

The development of a satisfactory intragastric camera capable of taking multiple photographs of the gastric lumen on colour film was carried out in Japan and was first reported in 1950 (Uji, 1950). The stimulus which led to the evolution of this instrument was the

need for a screening programme for the detection of early gastric cancer in Japan where the incidence of the disease is notoriously high, and where the physical characteristics of the population render gastroscopy difficult and hazardous (Hadley, 1965). The initial development of techniques for gastric photography (Tasaka and Ashizawa, 1958) resulted in the production of the Olympus gastro-camera, of which a number of models have been produced. A system has been evolved whereby a systematic photographic survey of the whole gastric mucosa can be accomplished using this instrument (Morrissey, Honda, Hara, Juhl and Perna, 1965), and a high degree of accuracy (of 80 - 90%) obtained in the diagnosis of discrete lesions of the stomach by this method (Chrysopathis, 1963; Perna, Honda and Morrissey, 1965; Sullivan, Friedman and Owens, 1967; Blendis, Cameron and Hadley, 1967).

Subsequent upon the parallel development of both fibreoptic gastroscopes and gastrocameras, a number of instruments are now available in which an intragastric camera is incorporated in the distal end of a fibrescope allowing the easy and accurate photography of lesions under direct vision. The value of the blind gastrocamera and the indications for its use have, as a result, become somewhat more limited. It is, however, an instrument of much smaller diameter than any fiberscope, is simple and safe to use, and does not require the training and experience needed for gastroscopy. It is still widely used in Japan for mass screening, while in the United Kingdom and America, its principal value is probably as an adjunct to radiology as an aid to the clarification of doubtful radiological lesions (Scarrow, 1967; Evans, 1967). Its value in the detection of atrophic gastritis has received scant attention in the English language literature, and gastric photography was therefore included

in the present study with a view to evaluating its usefulness in this context.

Material and methods

Gastric photography was carried out or attempted upon 56 patients included in the study. The instrument used was an Olympus Mark V gastrocamera (Olympus Optical Co.) (Fig. 22). The instrument consists of a camera, 35 mm in length and 11.5 mm in diameter, sited at the end of a flexible vinyl-covered tube 75 cm in length and of 8 mm diameter. At the proximal or operating end of the tube is a control box which is connected to an electric supply. The camera has a fixed focus lens of focal length 3.6 mm, no shutter being required, and a flash bulb adjacent to the lens. A prepacked cassette containing a roll of 5 mm Anscochrome colour film 300 mm in length is inserted into the camera prior to the examination. The control box contains a film winder which winds the film up the flexible tube as exposures are made, a button to actuate the flash, a lever which flexes or extends the camera up to 35 degrees in its long axis, and a nipple to allow for insufflation of air into the stomach. Using this instrument, up to 32 photographs may be taken at one examination.

Method

The patients were premedicated with atropine, 0.6 mg, 1 hour before the procedure in order to reduce salivation, but no hypnotic was given as a routine unless the patients were unduly apprehensive. Half an hour, and ten minutes prior to passage of the camera, they were instructed to suck a 10 mg benzocaine lozenge. The camera was passed with the patient lying in the left lateral position. After manually passing the instrument into the pharynx, the patient was encouraged to swallow and the instrument was then passed down the oesophagus into the stomach. The examination was conducted in a

Figure 22: The Olympus Mark V Gastrocamera.

semi-darkened room with the abdomen exposed. By this method it was readily possible to observe the flash of the camera flash light through the abdominal wall, and by so doing to establish the position of the camera in the stomach (Fig. 23). The camera was manoeuvred so that the light showed at the level of the umbilicus, and then by moving the patient's position, it was manipulated into the pyloric antrum. Air was insufflated and a series of 32 photographs taken, rotating the camera through 45^{o} between each exposure and gradually withdrawing the instrument so as to obtain a series of photographs of each quadrant of the stomach in 8 positions from the pyloric antrum to the body. At the conclusion of the examination, the instrument was withdrawn, the film removed in a darkroom, and sent away for processing.

The returned film consists of a strip of circular colour transparencies, each 5 mm in diameter. For easy viewing the film strips were cut into sections, each containing 5 or 6 exposures and mounted on a 5 x 5 cm mount of the type normally used for the mounting of 35 mm film transparencies. By this method the film could be projected using a 35 mm photographic projector, the whole sequence of film from each patient being thus viewed at one time (Kirkpatrick and Marshall, 1969).

Results

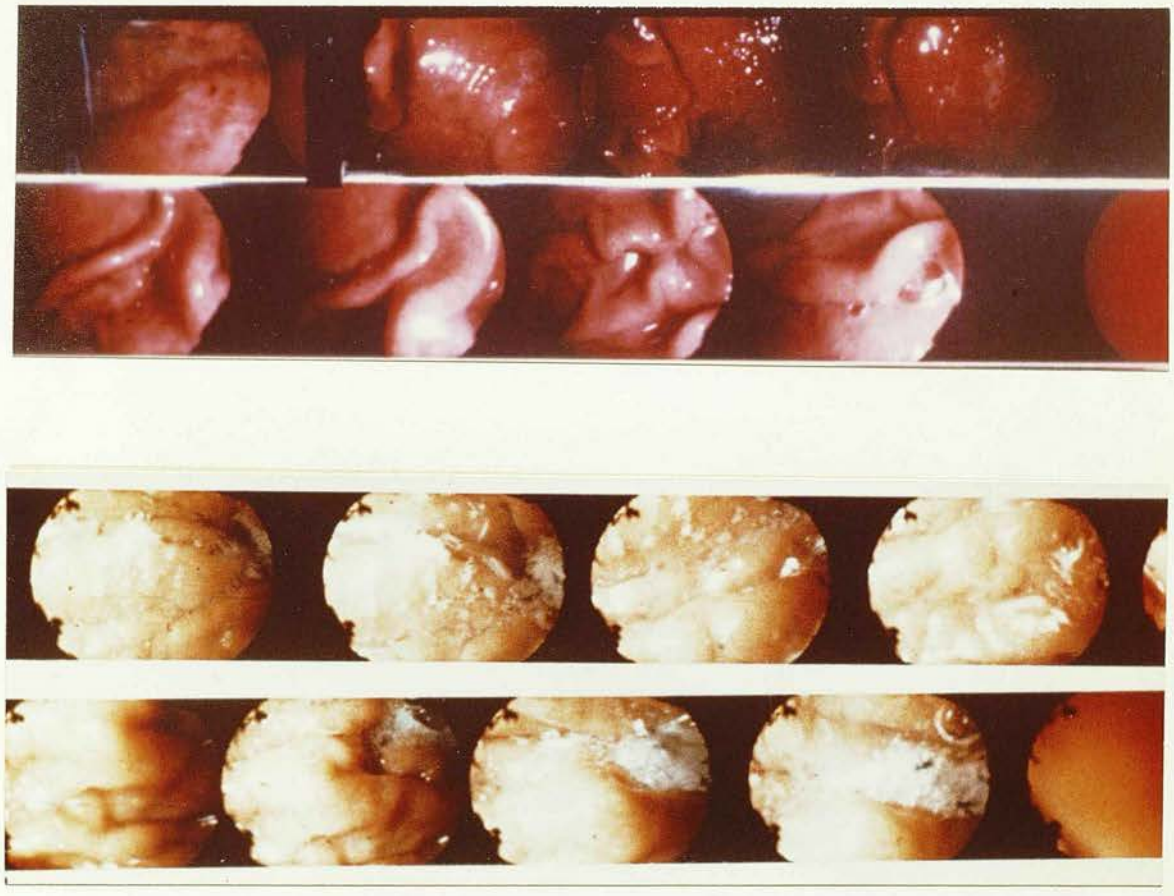
Gastric photography was attempted in 56 subjects. In 5 the instrument would not enter the stomach through the cardia, this occurring in 3 patients with high gastric carcinomata and in 2 others with no radiological evidence of mechanical obstruction at this level. In a further 6 the examination was unsuccessful. In 5 instances, photographs of poor quality were obtained showing insufficient detail on which an opinion could be based. In one instance the examination

Figure 23: Gastric photography in progress, the flash from the camera lamp being readily visualised through the abdominal wall.

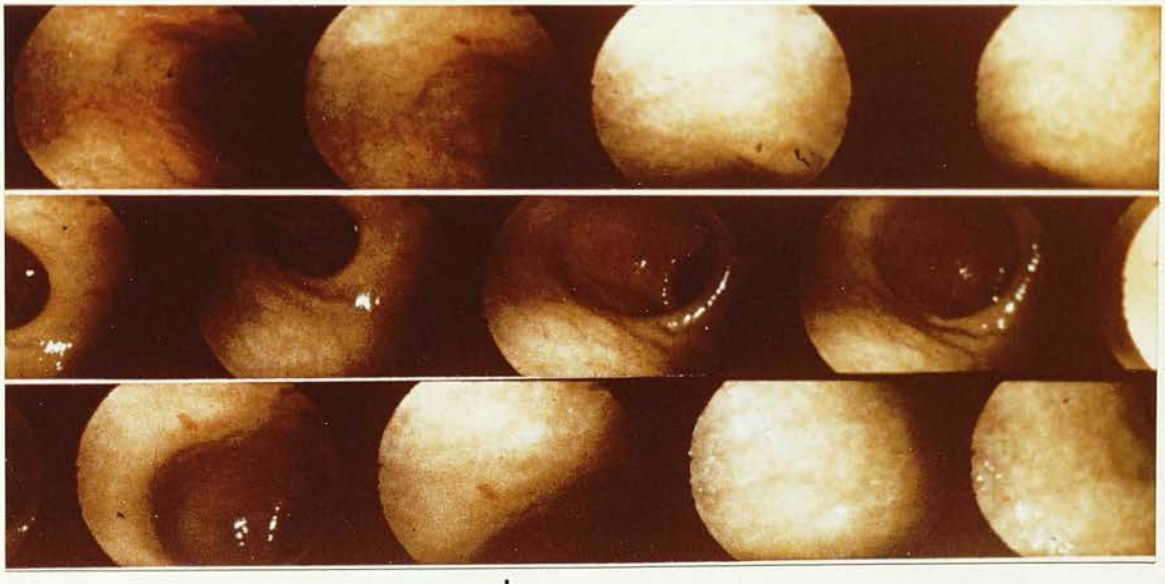
was abandoned at its outset as the patient had a brief episode of cardiac arrest as the stomach was being insufflated with air. The camera was at once removed and the patient immediately responded to external cardiac massage. It subsequently transpired that he had had several previous 'Stokes-Adams' seizures. No complication occurred in any other patient. There were thus 45 successful examinations, and the films from these patients were examined to assess the presence or absence of signs of atrophic change. The signs sought were those already discussed under the heading of 'Gastroscopy'. The films were examined by the author, and by 3 separate observers, 2 experienced gastroscopists and a radiologist, none of whom was at the time aware of the results of gastric biopsy. The results described and discussed below are based upon the conclusions reached at this examination, in which agreement was complete between all four observers.

1. Correlation between gastric photographs and gastric biopsy

Of the 45 successful gastrocamera examinations, 28 were performed upon patients with atrophic gastritis on biopsy, and 17 on patients with non-atrophic mucosa. Of those with atrophic gastritis, the photographs suggested the condition in 8 (29%), while in the remainder, the mucosa did not have an atrophic appearance (Fig. 24). Six of these 8 subjects had histologically severe atrophic gastritis out of a total of 16 with this grade of atrophic change, 37%, while 2 of 12 cases (17%) with mild or moderate changes had photographic evidence of the condition. Of the subjects with non-atrophic mucosa, the mucosa of 16 (94%) presented a normal appearance in the photographs. In the remaining 1 subject an atrophic appearance was seen, a false positive incidence, when compared with gastric biopsy, of 6% (Table LVI). This case had no other findings on gastroscopy, barium meal or acid output to suggest the condition.



a



b

Figure 24: Gastric photographs showing (a) a normal appearance of the gastric mucosa, and (b) the appearances of gastric mucosal atrophy.

Photographic assessment	Non-atrophic mucosa		Atrophic mucosa			Total
	Normal mucosa	Superficial gastritis	Atrophic gastritis Mild	Mod.	Severe	
Atrophic	1	0	2	0	6	9
Non-atrophic	11	5	5	5	10	36
Total	12	5	7	5	16	45
% agreement	92	100	40	0	37	
Accuracy %	94		29			

Table LVI: The assessment from gastric photographs of the presence or absence of atrophic gastritis in 28 patients with histologically proven atrophic gastritis and 17 with non-atrophic mucosa.

The overall agreement between gastric biopsy and the photographic assessment of the mucosa as to the presence or absence of atrophic change was 53% (Table LVII).

2. Correlation between gastric photographs and acid output

The mean maximal acid output of those cases in whom the photographs suggested atrophic gastritis, was 9.4 mEq/hour, and that of those with photographically normal mucosa was 12.6 mEq/hour. When compared using Student's 't' test these means did not differ significantly (Table LVIII). Of the 9 cases with atrophic gastritis on photographic assessment, 8 (89%) were hypochlorhydric, while normal values of acid output were found in 47% of those with apparently normal mucosa (Table LIX). Agreement between gastric photography and measurement of gastric acid output as indices of the presence or absence of atrophic gastritis was found overall in 55% of the 45 patients studied.

3. Correlation between gastric photographs and gastroscopy

Gastroscopy was performed in addition to gastric photography in 25 of the subjects. Of 6 in whom photography suggested atrophic gastritis, this was also found on gastroscopy in 4 (67%). Of 19 in whom the mucosa was deemed to be normal from study of the photographs, 10 (53%) were similarly assessed on gastroscopy, the remaining 9 having gastroscopic signs of atrophic gastritis (Table LX). The overall correlation between the two methods of examination as indices of the normality or otherwise of the mucosa was 56%.

4. Correlation between gastric photographs and radiology

A similar comparison was made between the findings on radiological examination and gastric photography in the 45 subjects who were photographed. Of the 9 in whom the photographs suggested atrophic change, radiological gastric atrophy was present in 5 (55%).

Photographic assessment	Biopsy		Total	% agreement
	Atrophic	Non-atrophic		
Atrophic	8	1	9	89
Non-atrophic	20	16	36	44
Total	28	17	45	
% agreement	29	94		53

Table LVII: The degree of agreement between the findings on gastric biopsy and gastric photography.

Photographic assessment	No.	Mean acid output (mEq/hour)
Atrophic	9	9.4
Non-atrophic	36	12.6

Table LVIII: The mean acid output in those patients with and without atrophic gastritis on gastric photography ($p < 0.4$).

Photographic assessment	Maximal acid output		Total	% agreement
	Atrophic	Non-atrophic		
Atrophic	8	1	9	89
Non-atrophic	19	17	36	47
Total	27	18	45	
% agreement	29	94		55

Table LIX: The degree of agreement between the maximal acid output (<10 mEq/hour as the index of atrophic gastritis) and the findings on gastric photography.

Photographic assessment	Gastroscopy		Total	% agreement
	Atrophic	Non-atrophic		
Atrophic	4	2	6	67
Non-atrophic	9	10	19	53
Total	13	12	25	
% agreement	31	83		56

Table LX: The degree of agreement between the mucosal findings on gastroscopy and on gastric photography.

Of the 36 with normal mucosa on photography, the mucosa was also radiologically normal in 29 (81%) (Table LXI). The overall correlation between the findings in the two examinations was 75%.

Discussion

Gastric photography as a means of recognising atrophic gastritis in this group of subjects was extremely unreliable. Although 37% of those with severe changes were detected, the condition was not recognisable in 71% of the total with biopsy evidence of atrophic change. On the other hand, 8 out of 9 cases considered to have atrophic gastritis had evidence of the condition on biopsy. This may be compared with 19 cases with photographic signs of this condition reported by Milton, Lynch and Skyring (1965) of whom the diagnosis was confirmed at biopsy in only 9, a false positive incidence of over 50%. Correlation with maximal acid output showed a similar trend, those with photographically atrophic mucosa being hypochlorhydric in all but one instance, while hypochlorhydria was found in 53% of those whose gastric photographs showed apparently normal mucosa. Agreement with gastroscopic findings and with the mucosal appearances on barium meal examination, while being less in those with positive photographic signs, was higher in those with apparently normal mucosa, especially in the case of radiology.

The reasons for the failure of gastric photography as a reliable means of assessing the state of the gastric mucosa, are probably largely those which have already been discussed in connection with gastroscopy, with inconstancy of inflation of the stomach and of distance from camera to image, with consequent variations in illumination. In gastroscopy these factors can, in part, be rectified during the examination, but with a blind procedure this is not possible. A further factor lies in the distortion which occurs with a wide angle

Photographic assessment	Radiology		Total	% agreement
	Atrophic	Non-atrophic		
Atrophic	5	4	9	55
Non-atrophic	7	29	36	81
Total	12	33	45	
% agreement	42	88		75

Table LXI: The degree of agreement between radiology and gastric photography as to the presence or absence of atrophic gastritis.

lens of the type used in the gastrocamera. Photographs taken at right angles to the surface of the object show considerable peripheral distortion while, when the camera is at an angle to the surface of the object, very considerable distortion results (Milton, Lynch and Skyring, 1965). Such distortion, while in no way interfering with the photography of discrete lesions, may well result on occasions in misleading photographs of the mucosal surface of the stomach.

CHAPTER 10

HAEMATOLOGY

The associations between both iron deficiency anaemia and pernicious anaemia, and atrophic gastritis, have already been reviewed and discussed in Chapter I. With a view to correlating haematological indices with the findings on gastric biopsy, and with other parameters indicative of atrophic change in the gastric mucosa, a series of haematological investigations were conducted upon the patients included in this study.

Materials and methods

Twenty-five ml of venous blood was taken from each patient and divided into five aliquots; one mixed with Sequestrene (di-potassium salt of ethylene diamine tetra-acetic acid) for estimation of haemoglobin concentration, mean cell haemoglobin concentration, mean cell volume and packed cell volume; one clotted specimen for determination of A.B.O. blood group; one clotted specimen for estimation of serum iron and iron-binding capacity; one clotted specimen for estimation of serum Vitamin B_{12}; and one clotted specimen for determination of parietal cell, intrinsic factor and thyroid antibodies.

The respective investigations were carried out in the Haematological Department, Cardiff Royal Infirmary, under the supervision of Dr. Allan Jacobs.

Methods

(a) Haemoglobin estimation. This was carried out by a photoelectric method diluting 0.02 ml of blood in 4 ml of 0.04% ammonia and matching the solution with a standard in a colorimeter (Dacie and Lewis, 1968). The haemoglobin concentration (Hb) was expressed in grams of haemoglobin per 100 ml of blood.

(b) Packed cell volume. The packed cell volume (PCV) was estimated by high speed centrifugation in micro-haematocrit tubes for 3-5 minutes and

the result expressed as a percentage of the total volume.

(c) Mean cell volume. This was calculated from the P.C.V. divided by the red-cell count in millions per cu.mm. (counted by electronic cell counter) and multiplied by 10. The result was expressed in cubic micra (cu.u.).

(d) Mean cell haemoglobin concentration. This value was calculated from the Hb in g. per 100 ml divided by the P.C.V. and expressed as a percentage.

(e) Serum iron. The serum iron concentration was estimated by the method of Ramsay (1957). Blood iron is almost entirely present in red cell haemoglobin but a small amount exists in the plasma as ferric iron forming a complex with a protein, transferrin, which migrates electrophoretically as a β globulin. In this test ferric iron is reduced using sodium sulphite as a reducing agent, and the ferrous iron so produced gives a pink colour in the presence of 2.2'-depyridyl. After the protein has been coagulated by boiling and by the addition of chloroform, the iron present in the centrifuged supernatant serum was estimated in a spectrophotometer against a known standard, and expressed in ug Fe per 100 ml of serum.

(f) Total iron binding capacity. This was estimated in combination with the estimation of serum iron (Ramsay, 1957). The iron binding protein transferrin is only partly saturated in the plasma with iron. By the addition of an amount of iron (5 µg per ml) more than sufficient to saturate the transferrin, the excess was adsorbed on to magnesium carbonate. The iron remaining in the serum was estimated as above and the total bound iron, and therefore the iron binding capacity (T.I.B.C.) calculated and expressed in µg per 100 ml. Knowing the serum iron value, the percentage saturation of transferrin can be readily calculated.

(g) Serum vitamin B_{12}. Assay of vitamin B_{12} is performed by a biological

assay method which depends upon the growth requirements of certain micro-organisms. The sera of the patients in this study were incubated with the Z strain of Euglena Gracilis (Hutner, Bach and Ross, 1956). The test sera were set up in triplicate in serial dilutions and incubated with a stock culture of the organism in a buffered medium for 3-4 days. The turbidity at the end of this period was read against a standard in a spectrophotometer, and the readings interpolated against a standard curve for vitamin B_{12} concentration and multiplied by the original dilution of the serum. The results were expressed in u ug per ml and represented the mean of 3 estimations on each specimen of serum.

(h) Parietal cell antibodies. Antibodies are gamma globulins, and rabbits immunised with human gamma globulin produce antibodies which react specifically with human gamma globulin. Rabbit anti-sera so produced can be conjugated with a fluorescent dye to produce a fluorescein-conjugated anti-human gamma globulin. Using this agent, microscopic examination in ultraviolet light reveals fluorescence wherever auto-antibodies adhere, be it to nuclei such as in systemic lupus erythematosus, or to cytoplasmic constituents as in auto-immune thyroiditis or the parietal cell in chronic atrophic gastritis.

Gastric mucosa was obtained from patients of blood group O undergoing gastric resection for peptic ulcer, and was immediately frozen in liquid nitrogen and stored at -20°C. Sections of the frozen gastric tissue were cut in a cryostat at 6 microns and dried in air. Sera from the patients were stored similarly at -20°C immediately after centrifugation. At the time of the test, sera were applied to the cryostat sections of mucosa for 30 minutes, the slides were then washed in buffered saline solution after which rabbit anti-human gamma globulin fluorescin conjugate was applied for 20 minutes.

After mounting, the sections were examined by ultraviolet microscopy. The presence of circulating auto-antibodies to parietal cells was recognised by bright green fluorescence in the cytoplasm of the parietal cells (Taylor, Roitt, Doniach, Couchman and Shapland, 1962). The results were recorded as positive or negative.

(i) Thyroid antibodies. The presence of thyroid antibodies in the sera of the patients studied was sought using an immuno-fluorescent technique, performed in a similar manner to the above, thyrotoxic thyroid tissue being substituted for gastric mucosa. The results were similarly recorded as positive or negative.

(j) Intrinsic factor antibodies. The presence of antibody to intrinsic factor was originally demonstrated by Taylor (1959) in the serum of patients with pernicious anaemia and a sensitive technique has been evolved by Ardeman and Chanarin (1963) for its detection. Antibody to intrinsic factor inhibits the uptake of Co^{60} labelled vitamin B_{12} by a mixture of human serum and normal gastric juice. A test serum, gastric juice containing intrinsic factor, and labelled vitamin B_{12} are incubated at room temperature and the radioactivity of the mixture is counted in a scintillation counter. The mixture is then shaken vigorously with washed activated charcoal which extracts unbound vitamin B_{12} and the radioactivity of the supernatant is measured again. The difference between the radioactive counts indicates the amount of unbound vitamin B_{12} and is a sensitive index of the presence or absence of intrinsic factor antibody. This test was carried out upon the sera of those patients in whom parietal cell antibody was found, and the results expressed as positive or negative.

(k) Blood group. The A, B, O blood group of each patient was

ascertained by the standard tube agglutination method (Dacie and Lewis, 1968). A cell suspension was added to each of three tubes containing respectively Anti A, Anti B and Anti A and B serum. After 2 hours incubation at room temperature the presence of agglutination was determined by inspection at the end of the period and the blood group determined.

(1) Faecal occult blood. The detection of occult blood in the stool depends upon the fact that the active group containing iron in haemoglobin can transfer oxygen from hydrogen peroxide to certain oxidizable substances such as orthotolidine to form a coloured dye.

The test was carried out using 'Haematest' tablets (Ames Co. Ltd.) which contain orthotolidine and peroxide. A smear of faeces was placed in the centre of a filter paper and a tablet placed over it and moistened with 2 drops of water. A blue colour appearing on the filter paper within 2 minutes was taken as being indicative of the presence of occult blood in the specimen. Results were expressed as positive or negative.

Results

Occult blood was found in the stool in 17 subjects who have been excluded from this section of the study, as it was felt that their haematological indices could be biased by overt blood loss. Similarly 9 cases of pernicious anaemia have been excluded. Some were under treatment at the time of the investigation and those awaiting treatment owed their haematological abnormality to the specific pathology of their disease. The study therefore relates to 81 subjects, except where otherwise stated. Of these, 33 had non-atrophic gastric mucosa and 48 had histologically demonstrated atrophic gastritis. Twenty-nine were female and 52 male. The normal values and ranges referred to are, unless otherwise stated, taken from

Dacie and Lewis (1968).

1. Absolute haematological indices

(a) Comparison with mucosal histology

The mean values for Hb, P.C.V., M.C.H.C. and M.C.V. (Table LXII) of men and women with non-atrophic and with atrophic gastric mucosa all fell within the normal range. The differences between the mean values of those with, and those without, atrophic mucosa were compared using Student's 't' test. No significant difference was found between the means except in the case of female patients with atrophic gastritis in whom the mean cell volume was significantly less than in those with normal mucosa.

Anaemia as judged by a haemoglobin concentration below the normal values ($<$ 13.5 g for males; $<$ 11.5 g for females) was found in 8 subjects, 4 male and 4 female. All had atrophic gastritis and comprised 17% of this group. In a similar way, the P.C.V. was found to be below the normal range ($<$40% for male; $<$ 35% for females) in 11 subjects, 1 with normal mucosa (3%) and 10 with atrophic gastritis (21%). The difference in the incidence of these indices of anaemia between the two groups was significant (X^2 = 5.65 and 5.31, $p < 0.02$ and < 0.05 respectively). The M.C.H.C. was below the normal range ($<$ 30%) in 4 (8%) of those subjects with atrophic gastritis and in none with non-atrophic mucosa, but this difference did not reach statistical significance (X^2 = 2.02, $p < 0.5 > 0.3$). The M.C.V. was found to be low ($<$76 um^3) in 1 subject with atrophic gastritis, but was above the normal range ($>$96 um^3) in 6 (18%) of the subjects with non-atrophic mucosa and in 8 (17%) of those with atrophic gastritis (Table LXIII).

Of the 81 subjects, 11 (13%) had one or more haematological indices indicative of anaemia. Ten (91%) of these subjects had

Index	Normal range	Sex	Non-atrophic mucosa ± S.D.	Atrophic mucosa ± S.D.	Mean diff.	t	p
Hb	13.5 - 18.0	M	15.6 ± 1.1	14.8 ± 1.3	0.8	1.763	>0.05
G/100 ml	11.5 - 16.5	F	13.3 ± 0.9	12.8 ± 2.7	0.5	0.512	>0.5
P.C.V.	40 - 54	M	45.5 ± 3.2	43.8 ± 5.0	1.7	1.410	>0.1
%	35 - 47	F	40.7 ± 2.7	38.8 ± 6.5	1.9	0.791	>0.4
M.C.H.C.	30 - 35	M	33.7 ± 1.4	33.1 ± 1.2	0.6	1.50	>0.1
%		F	32.5 ± 1.2	32.3 ± 3.0	0.2	0.19	>0.8
M.C.V.	76 - 96	M	89.7 ± 6.0	88.7 ± 10.0	1.0	0.40	>0.6
um^3		F	92.2 ± 7.6	85.3 ± 7.7	6.9	2.13	<0.05

Table LXII: The mean values of absolute haematological indices in subjects with non-atrophic and with atrophic gastric mucosa.

Index	Non-atrophic mucosa		Atrophic mucosa		X^2	p
	Male	Female	Male	Female		
Hb (low)	0	0	4 (15%)	4 (19%)	5.65	<0.02
P.C.V. (low)	1 (4%)	0	6 (22%)	4 (19%)	5.31	<0.05
M.C.H.C. (low)	0	0	1 (4%)	3 (14%)	2.02	<0.5
M.C.V. (high)	4 (16%)	2 (25%)	6 (22%)	2 (9%)	0.67	<0.8
(low)	0	0	1 (3%)	0		

Table LXIII: The incidence of pathological variations in absolute haematological values in subjects with non-atrophic and with atrophic gastric mucosa.

atophic gastritis. Thus, of 48 subjects with atrophic gastritis, anaemia was found in 21% compared with 3% of 33 with normal mucosa. The incidence of anaemia in subjects with atrophic gastritis differed significantly from that of those with normal mucosa ($X^2 = 5.22$ $p < 0.05$) (Table LXIV).

(b) Comparison with maximal acid output

The relationship between the haemoglobin concentration and M.C.H.C. and maximal acid output was studied by comparing the means of these indices in patients with an acid output in excess of 10 mEq/hour with those whose acid output fell below this figure. The findings in 85 patients were studied, those with occult blood in the stool, and those with pernicious anaemia being excluded. Four patients in whom gastric biopsies were not available have been included. Forty-two of these patients were hypochlorhydric and 43 had acid outputs within the normal range.

The mean haemoglobin concentration of those with an acid output in excess of 10 mEq/hour was 15.3 g per 100 ml compared with 13.4 g in those with hypochlorhydria. These means were compared using Student's 't' test and the difference found to be highly significant ($p < 0.001$; Table LXV). The mean values of P.C.V., M.C.H.C. and M.C.V. were almost identical, however, in the two groups.

Of the 85 patients, 10 had a haemoglobin concentration below the normal range. Of these, 9 were hypochlorhydric and one had an acid output in excess of 10 mEq/hour. Eleven had a P.C.V. below the normal range, of whom 10 were hypochlorhydric, and all 4 patients in whom the M.C.H.C. was less than 30% were hypochlorhydric. Thus, of 11 subjects in whom one or more absolute haematological values indicated significant anaemia, 10 (91%) were hypochlorhydric, while, of 42 hypochlorhydric patients 10 (24%) were anaemic, compared with 1 (2%)

Gastric mucosa	Anaemic	Not anaemic	Total
Atrophic	10 (21%)	38	48
Non-atrophic	1 (3%)	32	33
Total	11 (13%)	70	81

Table LXIV: The incidence of anaemia in subjects with atrophic gastric mucosa compared with those with non-atrophic mucosa ($X^2 = 5.2$; $p < 0.05$).

Acid output	No.	Mean Hb (G/100 ml) ± S.D.	Mean diff. ± S.E.	t	p
10 mEq/hour	42	13.4 ± 2.7			
			1.9 ± 0.45	4.22	<0.001
10 mEq/hour	43	15.3 ± 1.4			

Table LXV: The mean haemoglobin concentration in 42 hypochlorhydric subjects compared with that of 43 subjects with normal levels of acid output.

of subjects with normal acid outputs and no evidence of gastro-intestinal bleeding. These findings were analysed by the X^2 test and found to be significant ($X^2 = 8.9 \quad p < 0.01$) (Table LXVI).

2. Iron metabolism

(a) Comparison with gastric mucosal histology

The mean values for serum iron and total iron binding capacity were all within normal limits for men and women with and without histological atrophic gastritis. A significant difference was found between the mean serum iron levels of men and women, but no difference of significance was found in either value between those with and those without atrophic gastritis, in either sex or in the groups taken as a whole. The degree of saturation of the iron binding protein transferrin was significantly lower in women than in men but again no significant difference was found in the percentage saturation between those with and without atrophic gastritis (Table LXVII).

Employing a serum iron value of under 80 ug/100 ml, transferrin saturation of less than 20% or M.C.H.C. of less than 30% as an index of iron deficiency, evidence of iron deficiency was found in 7 (21%) of 33 subjects with non-atrophic mucosa and 15 (31%) of 48 patients with atrophic gastritis, 9 of whom had severe changes. The significance of these findings in the two groups was compared employing the X^2 tests and the difference was found to be not significant ($X^2 = 1.01 \quad p < 0.5 > 0.3$) (Table LXVIII). The incidence of iron deficiency in the 29 females studied was 41% however, and was significantly higher than in that found in males (19%) ($X^2 = 4.81 \quad p < 0.05$) (Table LXIX). In neither sex, however, were significant differences found between the incidence of iron deficiency in those with atrophic and those with non-atrophic mucosa (Tables LXX and LXXI).

Acid output	Anaemic	Not anaemic	Total
10 mEq/hour	10 (24%)	32	42
10 mEq/hour	1 (2%)	42	43
Total	11 (13%)	74	85

Table LXVI: The incidence of anaemia in subjects whose maximal acid output was above or below 10 mEq/hour ($X^2 = 8.9$; $p < 0.01$).

Value	Normal range	Sex	Gastric mucosa		Mean diff.	t	p
			Non-atrophic ± S.D.	Atrophic ± S.D.			
Serum Fe ug/100 ml	80 - 180	M	117.4 ± 40.6	115.5 ± 46.6	1.9	0.15	>0.9
		F	92.3 ± 7.6	92.6 ± 50.1	0.3	0.02	>0.9
T.I.B.C. %	250 - 400	M	367 ± 52	377 ± 80	10	0.48	>0.6
		F	417 ± 155	405 ± 106	12	0.24	>0.8
Transferrin saturation %	50 - 20	M	32 ± 10	32 ± 15	0	0.08	>0.9
		F	21 ± 7	24 ± 13	3	0.51	>0.6

Table LXVII: The mean values of Serum Fe, T.I.B.C., and Transferrin saturation in subjects with non-atrophic and with atrophic gastric mucosa.

Gastric mucosa	Iron deficient	Not iron deficient	Total
Atrophic	15 (31%)	33	48
Non-atrophic	7 (21%)	26	33
Total	22 (27%)	59	81

Table LXVIII: The incidence of iron deficiency in subjects with atrophic and non-atrophic gastric mucosa ($X^2 = 1.01$; $p > 0.3$).

Sex	Iron deficient	Not iron deficient	Total
Male	10 (19%)	42	52
Female	12 (42%)	17	29
Total	22 (27%)	59	81

Table LXIX: The incidence of iron deficiency in male and female subjects irrespective of mucosal histology ($X^2 = 4.81$; $p < 0.05$).

Gastric mucosa	Iron deficient	Not iron deficient	Total
Atrophic	6 (22%)	21	27
Non-atrophic	4 (16%)	21	25
Total	10 (19%)	42	52

Table LXX: The incidence of iron deficiency in males with atrophic and with non-atrophic mucosa ($X^2 = 0.38$; $p > 0.5$).

Gastric mucosa	Iron deficient	Not iron deficient	Total
Atrophic	9 (43%)	12	21
Non-atrophic	3 (38%)	5	8
Total	12 (42%)	17	29

Table LXXI: The incidence of iron deficiency in females with atrophic and non-atrophic mucosa ($X^2 = 0.5$; $p > 0.3$).

(b) Comparison with maximal acid output

As in the case of absolute haematological values, 85 patients were studied, of whom 42 were hypochlorhydric and 43 had acid output levels in excess of 10 mEq/hour. The mean serum iron levels were compared for each group. Of those subjects whose acid output exceeded 10 mEq/hour, the mean serum iron was 112.9 ug/100 ml compared with 100.7 ug/100 ml in those with hypochlorhydria. The difference between these means was compared using Student's 't' test and was found not to be significant ($p < 0.2 > 0.1$). Two further indices of iron deficiency, namely transferrin saturation and M.C.H.C. were similarly compared. No significant difference was found between the means of either value ($p > 0.1$ and > 0.05 respectively) (Table LXXII).

Employing a serum iron level of less than 80 ug/100 ml, transferrin saturation of less than 20% or M.C.H.C. of less than 30% as indices of iron deficiency, this was indicated in 22 subjects. Of the 43 subjects with normal levels of acid output 7 (16%) were iron deficient compared with 15 (36%) of 42 hypochlorhydric subjects. These findings were compared employing the X^2 test and were found to be significant ($p < 0.05$) (Table LXXIII).

It may be said, therefore, that while iron deficiency was only present in 31% of subjects with atrophic gastritis and 36% with hypochlorhydria, the finding of iron deficiency in the absence of clinical evidence of blood loss was associated with atrophic gastritis and hypochlorhydria in 70% of the subjects in whom it was found.

3. Vitamin B_{12}.

(a) Comparison with mucosal histology

The mean serum vitamin B_{12} levels of 61 subjects with atrophic gastritis and 37 with non-atrophic mucosa were compared. The mean for

	Acid output >10 mEq/hr.	Acid output <10 mEq/hr.	Mean diff.	S.E.	t	p
No. of patients	43	42				
Mean serum Fe ug/100 ml ± S.D.	112.9 ± 43.3	100.7 ± 48.4	12.2	± 9.95	1.23	0.2
Transferrin saturation % ± S.D.	30.1 ± 6.3	27.2 ± 8.4	2.9	± 1.7	1.53	>0.1
M.C.H.C. % ± S.D.	33.4 ± 1.3	32.6 ± 2.7	0.8	± 0.45	1.77	>0.05

Table LXXII: The mean value of three indices of iron deficiency compared in subjects with normal levels of acid output and with hypochlorhydria.

Acid output	Iron deficient	Not iron deficient	Total
$<$ 10 mEq/hour	15 (36%)	27	42
$>$10 mEq/hour	7 (16%)	36	43
Total	22 (26%)	63	85

Table LXXIII: The incidence of iron deficiency in subjects whose maximal acid output was above or below 10 mEq/hour ($X^2 = 4.19$; $p < 0.05$).

those with atrophic change was 257 uug per ml compared with 301 in the non-atrophic group. Both means fell within the normal range of 120 - 650 uug/ml., and when compared using Student's 't' test differed insignificantly ($p > 0.05$) (Table LXXIV). The mean value for 64 males was 267 $\pm$ S.D. of 125 and for 34 females 271.8 $\pm$ S.D. of 117. These means did not differ significantly.

In 6 subjects the serum vitamin B_{12} lay below 120 uug/ml and when repeated the result remained below this figure. All these subjects were fully investigated by Vitamin B_{12} absorption test and marrow biopsy and none was found to have pernicious anaemia. All had atrophic gastritis, 3 severe, 1 moderate and 2 mild, on gastric biopsy. Three had iron deficiency anaemia (one associated with carcinoma of the stomach and melaena), 3 had parietal cell antibody and one intrinsic factor antibody in the serum. A further subject with gastric carcinoma had a serum vitamin B_{12} level of under 120 uug/ml but did not have a gastric biopsy performed and the Schilling test was not carried out (Table LXXV).

(b) Comparison with maximal acid output

The mean serum vitamin B_{12} level for those subjects with hypochlorhydria was compared with that of those with normal levels of acid output. Of 52 subjects whose acid output lay below 10 mEq/hour, the mean B12 value was 260 uug per ml compared with 293 uug per ml in 48 with acid outputs in excess of that value. These means were compared employing Student's 't' test and were not found to differ significantly (Table LXXVI).

Of the 6 subjects in whom the serum vitamin B_{12} was less than 120 uug per ml., 5 were hypochlorhydric and one had an acid output in the normal range. Thus 5 (11%) of hypochlorhydric patients and 1 (2%) of patients with normal acid output had serum vitamin B_{12} levels below

	Non-atrophic mucosa	Atrophic mucosa	Mean diff.	S.E.	t	p
No. of subjects	33	48				
Mean serum vitamin B_{12} uug/ml $\pm$ S.D.	301 $\pm$ 124	257 $\pm$ 124	44	28.03	1.73	>0.05

Table LXXIV: The mean serum vitamin B_{12} levels in 33 patients with non-atrophic and 48 patients with atrophic gastric mucosa.

Serum Vit. B_{12} uug/ml	Sex	Diag-nosis	Hb G/100 ml	M.C.V. cu	Serum Fe ug/100 ml	P.C.A.	Acid output mEq/hr.	Gastric biopsy
101	M	N.U.D.	15.8	104	75	-	7.6	Mild A.G.
94	F	Ca.	9.2	72	40	+	7.6	Mild A.G.
106	M	G.U.	15.2	95	110	-	19.6	Moderate A.G.
98	M	N.U.D.	16.3	97	130	+	0.0	Severe A.G.
72	F	N.U.D.	14.5	86	75	-	0.0	Severe A.G.
102	M	N.U.D.	15.2	95	180	+	0.0	Severe A.G.
102	M	Ca.	4.7	69	40	-	0.0	Not done

Table LXXV: Clinical and laboratory parameters of patients presenting with low serum Vitamin B_{12} levels. All patients were in the age range of 49 - 73 years. Intrinsic factor antibodies were not found in any case. Schilling test revealed no evidence of Vitamin B_{12} malabsorption in any subject.

	Acid output >10 mEq/hr.	Acid output <10 mEq/hr.	Mean diff.	S.E.	t	p
No. of subjects	42	41				
Mean serum Vitamin B_{12} uug/ml ± S.D.	293 ± 88	260 ± 123	33	23.8	1.40	>0.1

Table LXXVI: The mean value of the serum Vitamin B_{12} in subjects with normal levels of acid output compared with those with hypochlorhydria.

the normal range.

4. Parietal cell antibodies

Parietal cell antibodies were found in the sera of 16 of the 111 patients upon whom this investigation was carried out. They were found in 6 (66%) of 9 patients with pernicious anaemia, in 10 (17%) of 62 patients with atrophic gastritis, and in no patient with non-atrophic gastric mucosa. Of the atrophic gastritis subjects exhibiting this antibody, 7 were female (27% of 27 subjects) and 3 were male (9% of 35 subjects). Four had severe atrophic gastritis, 4 moderate and 2 mild changes in the gastric mucosa. Six of the patients had non-ulcer dyspepsia, 2 gastric carcinoma and 2 benign gastric ulceration. Three females had iron deficiency but this was not present in the remaining 7 subjects. Intrinsic factor antibodies were found in 2 of the 6 pernicious anaemia patients and in 2 patients with atrophic gastritis, neither of whom had evidence of vitamin B_{12} deficiency. Thyroid antibodies were present in the sera of 9 patients with parietal cell antibodies, 5 with pernicious anaemia, and 4 with simple atrophic gastritis (Table LXXVII).

5. Thyroid antibodies

Thyroid cytoplasmic antibodies were found in the sera of 23 of the 111 patients upon whom the investigation was performed. As already stated, they were found in 5 (55%) of 9 subjects with pernicious anaemia, two of whom had, in addition, antibody to intrinsic factor. Of the remaining 18 subjects exhibiting thyroid antibody, 13 had atrophic gastritis (21% of 62 studied) and 5 had non-atrophic mucosa (12.5% of 40 studied). This difference was not significant ($X^2 = 1.27$ $p > 0.2$). Excluding patients with pernicious anaemia, thyroid antibodies were found in 9 (35%) of 36 women and in 9 (13%) of 67 men, the

Sex	Diagnosis	Hb G/100 ml	Serum Fe ug/100 ml	Serum Vit. B_{12} uug/ml	I.F.A.	T.A.	Acid output mEq/hr.	Gastric biopsy
F	P.A.				+	+	0.0	Gastric atrophy
F	P.A.				+	+	0.0	Moderate A.G.
M	P.A.				-	-	0.0	Gastric atrophy
M	P.A.	6.0	185	17	-	+	0.0	Severe A.G.
M	P.A.	12.7	100	46	-	+	0.0	Severe A.G.
M	P.A.	6.9	175	29	-	+	0.0	Severe A.G.
M	N.U.D.	16.3	130	98	-	-	0.0	Severe A.G.
F	N.U.D.	10.5	35	211	-	-	0.0	Severe A.G.
F	N.U.D.	15.7	145	386	-	-	3.9	Severe A.G.
F	N.U.D.	14.8	105	204	-	-	5.9	Moderate A.G.
F	N.U.D.	13.9	120	206	+	+	0.0	Moderate A.G.
M	N.U.D.	15.2	180	102	-	-	0.0	Severe A.G.
M	Ca.	16.4	100	279	-	+	14.6	Moderate A.G.
F	Ca.	9.2	40	94	-	+	9.2	Mild A.G.
F	G.U.	15.7	160	163	-	-	12.2	Moderate A.G.
F	G.U.	13.9	45	208	+	+	6.0	Mild A.G.

Table LXXVII: Clinical and laboratory parameters of 16 subjects with parietal cell antibodies in the serum. The subjects were in the age range of 49-73 years.

difference being statistically insignificant (X^2 = 1.91 $p > 0.2$).

6. Blood group

A.B.O. blood group were ascertained in 113 subjects, from whom gastric biopsies had been taken in 109. The distribution of blood groups in the 113 subjects studied is shown in Table LXXVIII and is compared with the distribution in South Wales (Kopec, 1970). The distributions of group A, O, and B + A.B. did not differ significantly (X^2 = 0.30 $p > 0.5$). The numbers in group B and A.B. were too small for statistical analysis individually, and were combined. The A.B.O. blood group distribution of the 70 subjects with atrophic gastric mucosa and 39 with non-atrophic mucosa were compared (Table LXXIX). The distribution of blood groups A, O, and B +AB did not differ significantly (X^2 = 1.85 $p > 0.05$). The distribution in neither of these groups differed significantly from the South Wales distribution (X^2 = 0.005 and 0.37 $p > 0.9$ and >0.5 respectively).

Similar analyses were carried out with regard to the blood group distribution of patients with and without hypochlorhydria (Table LXXX). These distributions did not differ significantly with regard to blood group A, O, and B + AB (X^2 = 1.01 $p > 0.2$). Neither the hypochlorhydric group nor those with normal acid output levels differed significantly in blood group distribution from that found in South Wales (X^2 = 0.04 and 6.87 $p > 0.8$ and >0.3 respectively).

Although no significant differences were found, it will be seen from these tables that there was an increase in the proportion of subjects with blood group A in the presence of atrophic gastritis and hypochlorhydria, with a decrease in group B + A.B., and that there was an increase in the proportion of subjects with blood group

	No.	Blood group A	Blood group 0	Blood group B + AB
Present study	113	43 (38.0%)	55 (48.6%)	15 (13.3%)
South Wales (Kopec, 1969)	8472	40%	46%	14%

Table LXXVIII: The distribution of blood groups A, 0, and B + AB in the whole group under study compared with the distribution in South Wales (Kopec, 1969) ($X^2 = 0.30$; $p > 0.5$).

	No.	Blood group A	Blood group 0	Blood group B + AB
Atrophic mucosa	70	28 (40%)	33 (47.1%)	9 (12.9%)
Non-atrophic mucosa	39	13 (33.3%)	20 (51.3%)	6 (15.4%)

Table LXXIX: The distribution of blood groups A, 0, and B + AB in subjects with atrophic gastritis and with non-atrophic mucosa ($X^2 = 1.85$; $p > 0.05$).

	No.	Blood group		
		A	O	B + AB
Acid output <10 mEq/hour	65	28 (43.0%)	30 (46.2%)	7 (10.8%)
Acid output >10 mEq/hour	48	15 (31.2%)	25 (52.1%)	8 (16.7%)

Table LXXX: The distribution of blood groups A, O, and B + AB in subjects with hypochlorhydria, and those with normal levels of acid output ($X^2 = 1.01$ $p > 0.2$).

O in the presence of normal mucosa and normal acid output levels with a decrease in group A, when these subject groups are compared both with the total and their respective reciprocals.

Discussion

Hypochromic anaemia in the United Kingdom is almost invariably due to iron deficiency (Jacobs, Kilpatrick and Withey, 1965) and is characterised by a reduction in both the number and haemoglobin content of circulating red blood cells. The early stages of iron deficiency may be only indicated by a reduction in the level of serum iron and degree of saturation of the iron binding protein, transferrin, and may not be reflected in a reduction in the absolute haematological indices. Anaemia develops when the amount of iron available for haemoglobin in the bone marrow is inadequate and this only occurs when the amount of stored iron in the body is low. The common causes of iron deficiency are chronic blood loss in excess of iron intake, or in excessive menstrual loss or bleeding from the gastrointestinal tract, or inadequate dietary intake. Fry (1961) could find no apparent cause for iron deficiency in 53% of men and 87% of women with anaemia in his general practice. The interaction between iron deficiency and hypochlorhydria has already been discussed in Chapter 2.

In the group of patients in this study, occult blood was found in the stool in 21 subjects and this was associated with anaemia or latent iron deficiency in 20. Iron deficiency was found in 22 (30%) of the 81 subjects in whom no blood loss was demonstrated (19% of males and 42% of females). Of these, 8 (36%) were anaemic as judged by a Hb concentration below the normal levels (8% of males and 14% of females). This incidence of anaemia may be compared with that found in a South Wales population of 600 men over the age of 35 and 200 women over the age of 55, of whom 3% of the men and 14% of the women

were anaemic (Kilpatrick and Hardisty, 1961). The incidence of iron deficiency in a group of 500 women from a broad spectrum of age range was found by McFarlane, Pinkerton, Dagg and Goldberg (1967) to be 21%, compared with an incidence of iron deficiency anaemia of 8.2%, and in 333 elderly hospital patients, Powell, Thomas and Mills (1968) found iron deficiency without anaemia in 39% of men and 41% of women.

Of the 8 anaemic patients, as judged by haemoglobin concentration, all had atrophic gastritis on gastric biopsy and of 11 in whom one or more absolute haematological indices indicated anaemia, 10 (91%) had atrophic gastritis and also hypochlorhydria. These findings are in keeping with those of Shearman, Delamore and Gardner, who found hypochlorhydria in 12 (70%) of 17 anaemic patients of whom 4 of the 5 with acid output levels in excess of 10 mEq/hour had evidence of overt blood loss.

In this study the incidence of iron deficiency in those with and those without atrophic gastritis, did not differ significantly, and the incidence of atrophic gastritis was not significantly higher in the iron deficient group compared with those without iron deficiency. However, when acid output was compared with iron deficiency, a significant correlation was found between hypochlorhydria and the presence of iron deficiency. In a comparable study, Davidson and Markson (1955) found that of 42 patients with iron deficiency, 43% had atrophic mucosa (68% in the present study), while of 31 non-iron deficient controls, atrophic mucosa was found in only 23%, compared with 56% in the present study. These workers also found achlorhydria in 48% of their iron deficient patients and in 13% of their non-iron deficient controls. The disparity between the correlation of iron deficiency with hypochlorhydria and with atrophic change in the present study requires explanation. While 70% of iron deficient

subjects had both atrophic mucosa and hypochlorhydria, a higher percentage of non-iron deficient patients had atrophic gastritis (56%) than had hypochlorhydria (43%) suggesting once again that patchy atrophic gastritis may have been present in those patients in whom the finding of atrophic mucosa was found in association with normal levels of acid output.

It may therefore be concluded that atrophic gastritis is found in the majority of patients with iron deficiency, but that these mucosal changes are by no means confined to such patients. The finding of unexplained iron deficiency requires full investigation, and this is likely to lead to the detection of atrophic gastritis.

It has been shown (Mollin, 1959; Wood, Cowling, Ungar and Gray, 1960) that in progressive atrophic gastritis, there may be a slow reduction in the production of intrinsic factor with failure of absorption of Vitamin B_{12} with depletion of stores of this vitamin in the liver, leading to a gradual fall in its serum levels. Cases have been recorded where such a situation has ultimately led to overt pernicious anaemia (Robertson, Wood and Joske, 1955; Siurala and Seppala, 1960). The incidence of atrophic gastritis has been shown to increase with age, and several groups of workers (Mollin and Ross, 1952; Boger, Wright, Strickland, Gylfe and Ciminera, 1955; Kilpatrick and Withey, 1965) have shown that a gradual fall in serum Vitamin B_{12} levels occurs with advancing years when means of large numbers are compared. No such pattern was found in the 101 subjects without pernicious anaemia in this study in whom the serum Vitamin B_{12} was estimated (Fig. 25). Of the 5 subjects in whom abnormally low serum Vitamin B_{12} levels were found, all were over 60 years of age and all but one had moderate or severe atrophic changes on gastric biopsy. One had mild atrophic gastritis

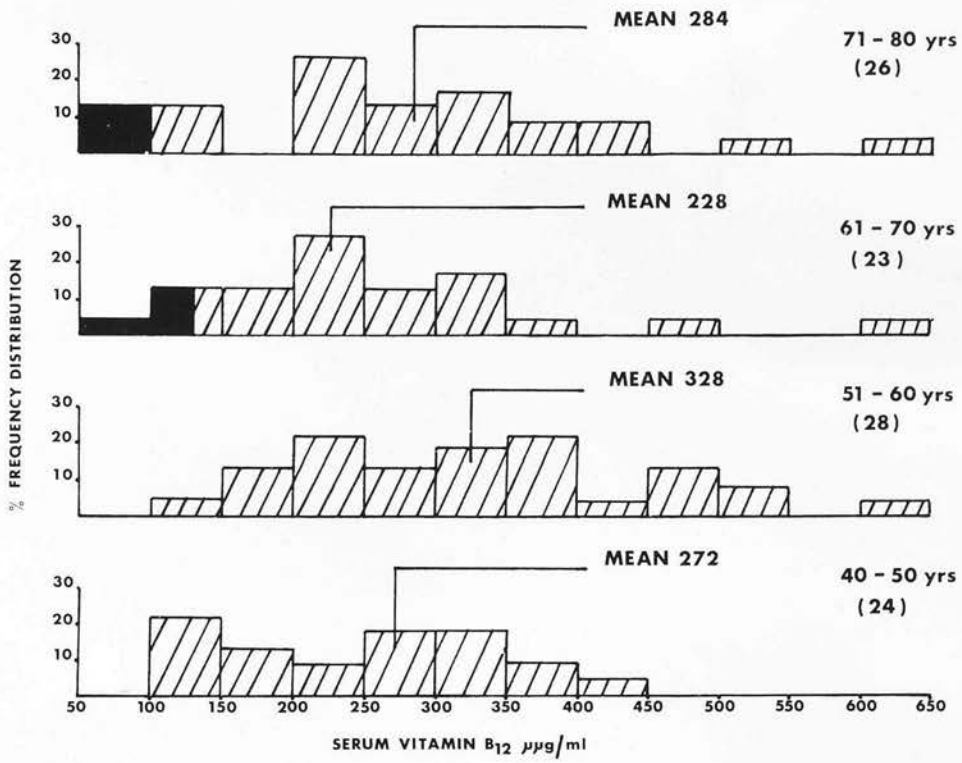


Figure 25: The frequency distribution of serum Vitamin B_{12} levels according to age in 101 subjects without pernicious anaemia.

and an acid output of over 10 mEq/hour. One of these patients had gastric carcinoma, involving the pyloric antrum and one a benign lesser curvature gastric ulcer. The other three, two males and one female, had no focal gastric lesion. Two patients had iron deficiency without anaemia, while a third, with gastric carcinoma, had positive occult blood in the stool, iron deficiency anaemia, parietal cell antibody in the serum and moderate atrophic gastritis on biopsy (Table LXXV). In the small number of subjects with low serum Vitamin B_{12} levels, therefore, no pattern was seen to associate this finding with any specific set of clinical, laboratory or other findings. The finding of this small group of subjects, however, underlines the importance of estimating the serum Vitamin B_{12} in patients with atrophic gastritis in order that those with low levels may be detected, investigated and followed-up. This is not only important in the context of the early detection and treatment of pernicious anaemia, but also to augment the present scanty information concerning the relationship between this disease and chronic atrophic gastritis.

The incidence of parietal cell antibodies in the serum has not been extensively investigated in population groups and most published figures relate to selected subjects. In a South Wales random survey, however, Jacobs (1968) found parietal cell antibodies in the sera of 126 (12.8%) of 982 people, 7.2% of 481 males and 18% of 501 females. The incidence rose with increasing age. Under the age of 45 P.C.A. was found in 6% of males and 12% of females and in those over 45 it was found in 8% of males and in 23% of females. The immuno-fluorescent tests were carried out in the same laboratory using identical methods as those in connection with the present study and may be used for comparison. They were not correlated with acid

output values or gastric biopsy and therefore may represent the incidence of autoimmune gastritis in the population from which they derive. They cannot be looked upon as being a control series. Excluding subjects with pernicious anaemia, the incidence in the present study was 4.3% of males and 20% of females, compared with 8% and 23% in Jacob's subjects over 45 years of age.

The incidence of P.C.A. of 67% in patients with pernicious anaemia is somewhat lower than the more generally accepted incidence of 80 - 90% quoted by Taylor (1965) and Coghill, Doniach, Roitt, Mollin and Wynn Williams (1965), who found an incidence of intrinsic factor antibody in 54% and 27% of their pernicious anaemia patients compared with 22% in the present study. They found thyroid cytoplasmic antibodies in 59% and 60% respectively of their pernicious anaemia patients compared with 55% in the present study.

Parietal cell antibodies were not found in the sera of any subject with non-atrophic gastric mucosa. Excluding subjects with pernicious anaemia, the incidence of P.C.A. of 9% in males and 27% in females compares with 12% and 61% found by Coghill and his co-workers. Markson and Moore (1962), Delamore and Shearman (1965), Wright, Whitehead, Wangel, Salem and Schiller (1966) and others, have shown, however, that the frequency with which parietal cell antibody is found is closely related to the nature of the accompanying disease, and that, apart from pernicious anaemia, its incidence is highest in the presence of iron deficiency. The latter authors have further shown that in patients whose gastric mucosa shows the features of atrophic gastritis but in whom iron deficiency is absent, the incidence of antibody is no higher than in a control population. Te Velde, Hoedemaker, Anders, Arends and Niewig (1966) subdivide chronic atrophic gastritis into two distinct types, the one 'patchy atrophic

gastritis', in which antibodies to parietal cell are not found, and Vitamin B_{12} metabolism is normal, the other 'diffuse atrophic gastritis' which may proceed to gastric atrophy and in which P.C.A. is frequently found and Vitamin B_{12} uptake often impaired. All writers stress the significant preponderance of females exhibiting P.C.A. in their sera.

Of the 10 subjects with atrophic gastritis in whom P.C.A. was found, iron deficiency was present in 3 (30%) and serum Vitamin B_{12} was low in a further 3. In two others, intrinsic factor and thyroid cytoplasmic antibodies were present in addition to P.C.A., suggesting the likelihood of pernicious anaemia developing in the future, despite normal blood values of Vitamin B_{12} at the present time. There were thus only two subjects of a total of 16 exhibiting P.C.A. in whom there was not evidence of either iron deficiency, or of pernicious anaemia or a disorder of the intrinsic factor/Vitamin B_{12} mechanism.

Of 15 subjects with atrophic gastritis and iron deficiency 3 (20%) had circulating P.C.A. These were all female patients and thus of the 9 female iron deficient subjects with atrophic gastritis, the incidence of P.C.A. was 33%.

Twenty-three of 111 subjects were found to have antibodies to thyroid cytoplasm. Of these, 9 (41%) also had parietal cell antibodies, a finding closely in accord with that of Taylor (1965) who found that the two antibodies co-existed in 52% of 79 patients with pernicious anaemia or autoimmune atrophic gastritis. Coghill and his co-workers found similar associations and stress the preponderance of females in which this is found. No significant female preponderance was found in this study.

It may be said therefore in regard to the finding of parietal cell antibodies in the serum, that this is always indicative of

atrophic gastritis and that it is likely to indicate the existence of iron deficiency anaemia or point to the presence of pernicious anaemia which may still be latent and which has developed against a genetic background in which thyroid disease, pernicious anaemia and possibly gastric carcinoma, are interwoven.

Observations from many countries have established that there exists a relationship between A.B.O. blood groups and the susceptibility to certain diseases, notably gastric cancer, gastric ulcer, duodenal ulcer and pernicious anaemia. Aird, Bentall and Roberts (1953) showed that the frequency of blood group A was greater, and that of blood group O smaller, in patients suffering from gastric cancer than in the general population from whence they derived, while Billington (1956), though not able to show such an association when all patients with gastric cancer were taken together, found a preponderance of blood group A in subjects with cancer of the pyloric antrum and cardia but not in those with body and fundus lesions in whom blood group O predominated. Several further studies have been published, some contradicting (Wallace, 1954) and others agreeing with Aird's findings (Køster, Sindrup and Seele, 1955; Buckwalter, Wholwend, Colter, Tidrick and Knowler, 1956). Fraser Roberts (1957), using a sophisticated statistical technique, was able to correlate these and other series and showed that there was an overall association between gastric cancer and blood group A and that there was an excess of group O in patients with gastric ulcers quoted in 7 published series from different parts of the world. Mosbech (1958) took the problem further when he showed that, while a significant increase in the frequency of blood group A was found in 1764 patients with gastric cancer, no differences were found between the percentage distribution of blood group in relation to sex, age of onset, tumour type, tumour

site, or gastric acidity, and Doll, Swynnerton and Newell (1960) were likewise unable to find any significant association between cancer site and blood group distribution. Pernicious anaemia has also been shown to be relatively more common in persons of blood group A than in those of group O (Hoskins and Zamcheck, 1965) and thus it would seem that these two conditions, both associated with gastric atrophy, the one malignant and the other with a malignant potential, show a common genetic preponderance, mediated by blood group A.

A further hereditary factor which may be involved in the aetiology of gastric cancer and peptic ulcer, is the secretor status of an individual, which is genetically determined independently of the A.B.O. group. Some 75% of persons secrete blood group substances A, B and H (A and H in group A secretor, B and H in group B secretors, AB and H in AB secretors, and H alone in group O secretors). Clark, Evans, McConnell and Shephard (1959) found a clear association between A, B, H non-secretors and duodenal ulcer, a relationship which is independent of, and of the same order of strength as for the group O association (Doll, Drane and Newell, 1961). These observations are parallel with other studies which have shown a greater liability for gastric cancer to occur among blood group A, and non-secretor subjects (Avery Jones, Gummer and Lennard Jones, 1968). Blood group substances are mucopolysaccharides and are found in saliva and gastric juice. Their mode of action is not clear, though it has been suggested that they may have an effect upon tissue resistance (Szulman, 1962). They do not affect gastric acid output (Hanley, 1964) and appear in the non-parietal component of gastric secretion (Evans, McConnell, Donohoe, Sircus and Crean, 1963).

The numbers of subjects in the present study are small but

showed no statistically significant deviation from the blood group distribution from the population whence they were derived. A tendency, however, was shown for there to be an increase in group A in the presence of atrophic mucosa and of group O in the presence of normal mucosa, but substantially larger numbers would be required for any meaningful conclusions to be drawn.

CHAPTER 11

GASTRIC EMPTYING IN ATROPHIC GASTRITIS

Griffith, Owen, Campbell and Shields (1968), employing an isotopically-labelled meal, showed that the rate of gastric emptying in a small group of subjects with malignant disease of the stomach was significantly slower than that of a contrast group of subjects without gastro-duodenal disease. The associations between atrophic gastritis and gastric cancer have already been discussed, and it therefore seemed appropriate to investigate the gastric emptying rate in patients with atrophic gastritis. In this study, which was conducted in association with Mr. W. T. Davies, Mr. G. M. Owen and Professor R. Shields, the gastric emptying rates of patients with atrophic gastritis and gastric cancer were studied, and compared with those of a contrast group of subjects free from gastro-duodenal disease.

De Salamanca (1949) and Hunt and Spurrell (1951) have shown that fluids leave the stomach in an exponential manner and have demonstrated dye dilution and serial test meal techniques for measuring the rate of gastric emptying of a fluid test meal. These methods do not however produce results which can be necessarily applied to a solid meal and, in addition, have the disadvantage of the need for nasogastric intubation during the investigation. More commonly, gastric emptying time is measured by noting the time taken for a radio-opaque meal to leave the stomach (Horton, Ross and Darling, 1965). This method however only measures the time when all of the meal has left the stomach. It has the further disadvantages that barium may separate from the food and leave the stomach at a different rate (Griffith, Owen, Campbell and Shields, 1966), that barium sulphate irritates the gastric mucosa and may affect the rate of emptying (Kirsh, 1956), and that the end point of gastric emptying may be obscured by barium adhering to the gastric mucosa.

Griffith, Owen, Kirkman and Shields (1966) introduced a new method of measuring the gastric emptying rate employing a standard meal of ordinary food, labelled with radioactive chromium (Cr^{51}) whose rate of disappearance from the stomach was measured by external counting. They demonstrated that the method was valid in that (a) radioactivity in the stomach could be clearly differentiated from that in the small bowel (b) that the external counting rate was independent of the depth of radioactivity within the body by mounting two detectors coaxially, one above and one below the table on which the patient lay (c) that the total count obtained was directly proportional to the radioactivity in the stomach, and (d) that dilution of the meal did not affect the external count. They showed, by plotting the logarithm and the square root of the counts obtained from the scans against time, that the fall of the external count was exponential for the major part of the emptying process. This finding, which was similar to that of Hunt and Spurrell (1951) suggested that the rate at which the meal left the stomach could be expressed as a single exponential function. The rate of gastric emptying was therefore expressed as the half-life of the meal in the stomach. Employing the half-life ($T\frac{1}{2}$) of the meal as the index of the emptying rate, they demonstrated that the method was reproducible from day to day in any individual. The dose of radiation to the patient was small, as Cr^{51} passes virtually unchanged through the alimentary tract with almost no absorption, and during decay almost all the energy released by Cr^{51} is contained in 0.32 MeV gamma rays, only a fraction of which is absorbed by the tissues.

Material and methods

Sixteen patients with atrophic gastritis were studied, the diagnosis of this condition being confirmed by biopsy of gastric body

mucosa. Multiple biopsies were obtained in 12 of these subjects, and a single biopsy from each of the remainder. None had any focal gastric or duodenal lesion, 4 had pernicious anaemia. The age range of these patients was from 41 - 74 years.

Ten patients with carcinoma of the stomach were studied, the growths being of varying size, type and histological grading. In no case was the pylorus obstructed by tumour. The ages of these patients ranged from 51 to 75 years.

Eleven contrast patients were investigated. These were patients free of overt gastro-duodenal disease admitted to a general surgical ward for treatment of minor complaints unrelated to the gastro-intestinal tract. Their ages ranged from 26 to 80 years with a mean age of 46 years. It was not considered ethically justifiable to submit these subjects to gastric biopsy.

In all cases permission for the study was obtained from the patients in accordance with the proposals laid down by the Medical Research Council (1962).

Methods

The rate of gastric emptying was determined by measuring the rate of disappearance from the stomach of a standard meal containing radioactive Cr^{51}. After fasting overnight, the patients were given a standard meal consisting of porridge (made from 20 g of oatmeal), two scrambled eggs, unskimmed milk and one slice of buttered bread. The meal was mixed in a liquidiser and to the mixture was added 200 uc of Cr^{51} in 5 ml of saline. The volume of the meal was 300 ml and it consisted of 31 g of fat, 26 g of protein and 42 g of carbohydrate.

The gamma rays emitted by the chromium were detected with an automatic scintiscanner fitted with 2 detectors, one above and one

below the table. The pulses were fed into a moving printer which printed a mark for a selected number of pulses on paper, thus indicating the distribution of radioactivity in the upper abdomen. The amount of radioactivity in the stomach at the time of each scan was measured by counting the number of marks within the outline of the stomach (Fig. 26). The first scan was carried out immediately after ingestion of the meal and scans were repeated at half-hour intervals until the stomach was empty. Between scans, the patients were allowed to walk about or sit in a chair.

The half-life ($T\frac{1}{2}$) of the meal was calculated by the method of least squares (Fig. 27) and this value was used as the index of the gastric emptying rate.

In 15 subjects with atrophic gastritis and in 9 with gastric carcinoma, the maximal acid output was measured after stimulation with 6 ug pentagastrin per kg body weight by the method already described in Chapter 6.

Results

Rate of gastric emptying (Fig. 28)

(a) Contrast group

The mean half-life ($T\frac{1}{2}$) of the meal in the stomach of 11 contrast patients was 45.6 minutes ($\pm$ S.D. of 5 minutes). The range of half-life was from 38 to 55 minutes.

(b) Atrophic gastritis

The mean half-life of the meal in these patients was 67.9 minutes ($\pm$ S.D. of 16.1 minutes) with a range of from 54 to 108 minutes. This mean was significantly greater than that of the contrast group when the two were compared employing Student's 't' test ($p < 0.05$).

(c) Carcinoma of the stomach

The mean half-life in this group of patients was 111.1 minutes

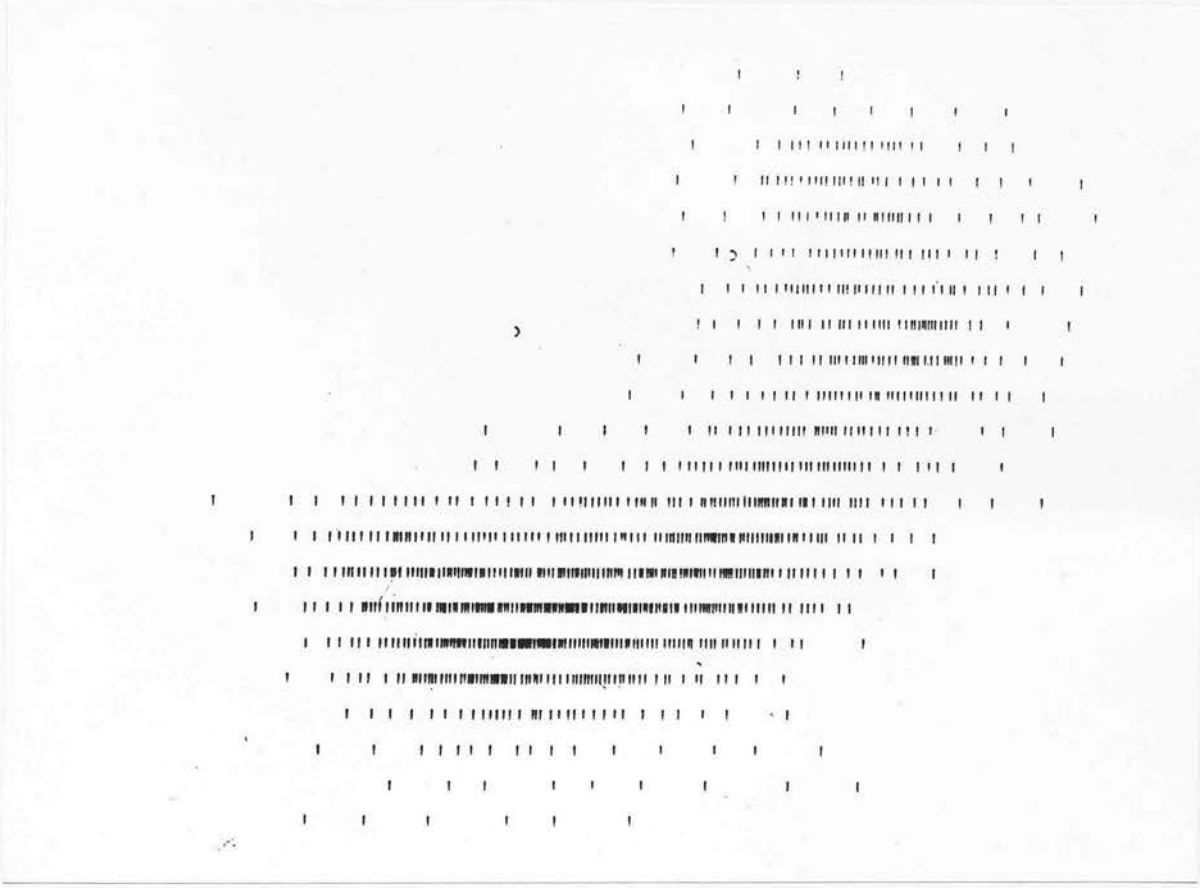


Figure 26: 'Print-out' of scintillation scan of the stomach shortly after ingestion of a standard meal containing radioactive Cr^{51}.

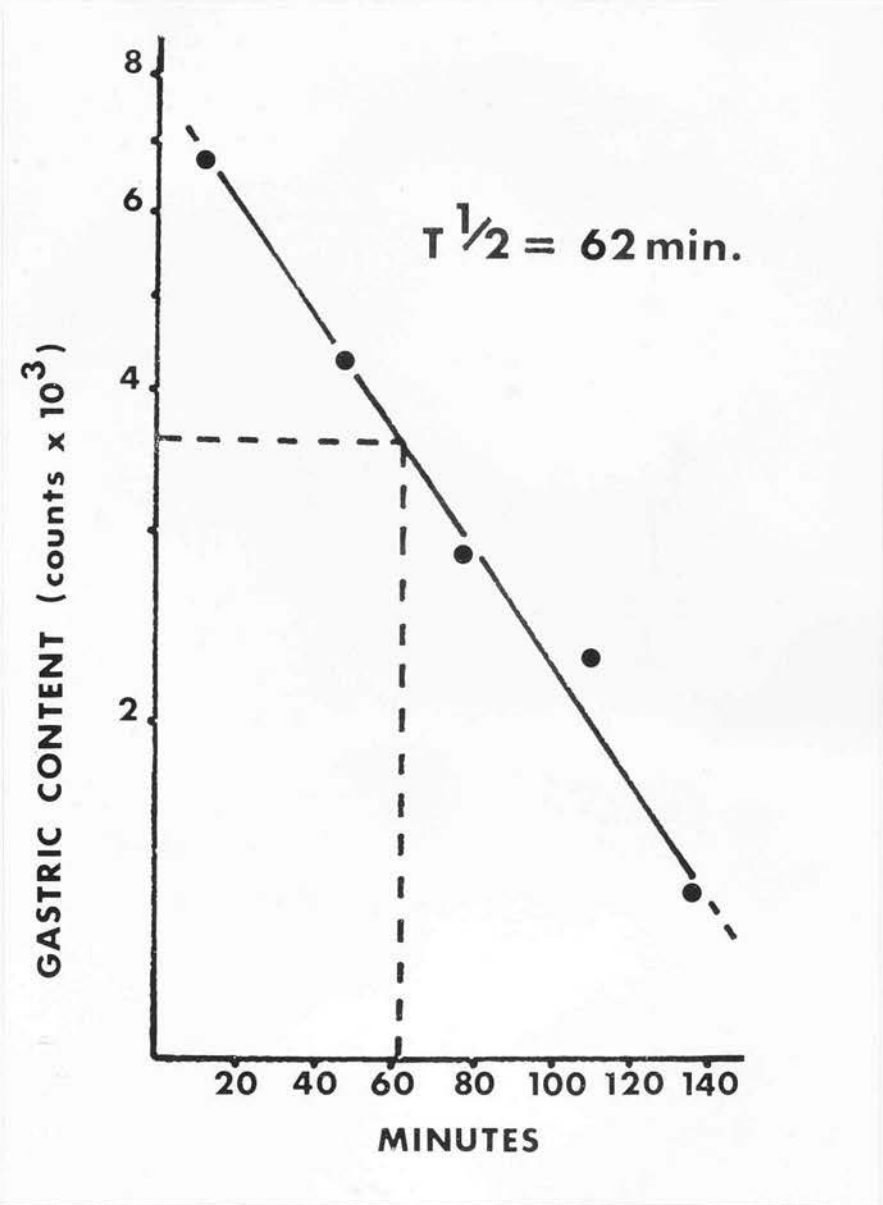


Figure 27: The rate of disappearance of Cr^{51} from the stomach expressed as the half-life of the meal ($T_{\frac{1}{2}}$).

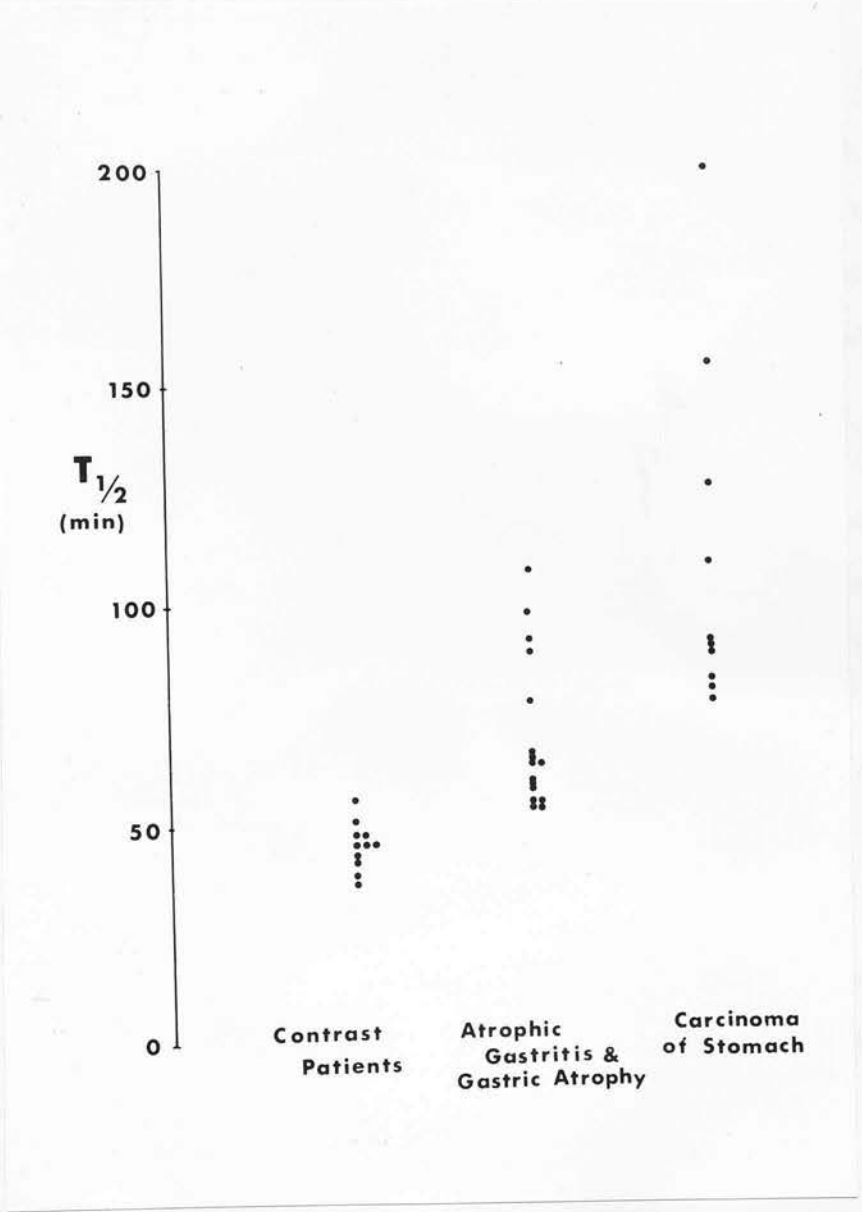


Figure 28: The range of gastric emptying rates found in control subjects and in subjects with atrophic gastritis and carcinoma of the stomach.

($\pm$ S.D. of 40 minutes) with a range of from 81 to 200 minutes. When compared with both the contrast group and the atrophic gastritis group, the mean half-life in these patients differed significantly from both ($p < 0.001$).

Relationship between gastric emptying and acid output (Fig. 29)

The secretion of acid tended to be less, and the rate of gastric emptying slower, in patients with gastric carcinoma when compared with those with atrophic gastritis but no significant correlation was found between these variables within or between the two groups.

Relationship between gastric emptying and age (Fig. 30)

It was not possible completely to match the ages of the subjects in all three groups. In the contrast group, however, no correlation was found between age and gastric emptying rate ($r = -0.028$; $p > 0.1$), and similar calculations revealed no significant correlation between these parameters in the other two groups of subjects.

Discussion

The striking finding in this study was the marked delay in gastric emptying in subjects with gastric carcinoma and, to a lesser but still significant degree, in those with atrophic gastritis. While low rates of acid secretion were found in both groups, no correlation was found between gastric emptying time and acid output. It is difficult to compare absolute rates of gastric emptying obtained by different methods, owing to the differing compositions of meals employed. Shay (1944) showed during radiological studies of gastric emptying that the stomachs of subjects with duodenal ulcer emptied faster than did those of control subjects, a

finding confirmed by Griffith and his co-workers (1968), using the chromium-labelled meal already described. Hunt (1957) on the other hand, using a serial fluid test meal method, did not detect such differences and indeed was of the opinion that the presence of acid reaching the duodenum caused inhibition of the gastric emptying process and that the rate of emptying was inversely related to the degree of acidity.

Further factors which may influence differences in the findings between differing techniques relate to the volume and composition of the test meal. Shay, Gershon-Cohen and Fels (1939), in reviewing mechanisms for the control of gastric secretion and emptying, showed that the presence of fat in the duodenum caused inhibition of gastric emptying, and Hunt (1961) demonstrated that increasing the osmolality of the duodenal content also reflexly slowed the gastric emptying rate. The osmotic pressure of the chromium-labelled meal was not measured but it is likely that it was substantially in excess of the fluid meal used by Hunt; this factor together with its high fat content may have overcome any pH-related inhibiting mechanism. Further, with a semi-solid 'physiological' test meal such as was used in the present study, considerable buffering of gastric acid could be expected. These factors probably account for the apparent anomaly between Hunt's findings and those reported in this thesis, in which no correlation between gastric acid secretory capacity and emptying rates was found. As has already been discussed, atrophic gastritis increases in prevalence with increasing age and the possibility that some of the contrast subjects might have atrophic gastritis cannot be excluded. Only one of these subjects was, however, over 60 years of age, the mean age being 46 years, and no evidence was found of any correlation between gastric emptying rate and age in any of the groups. It would

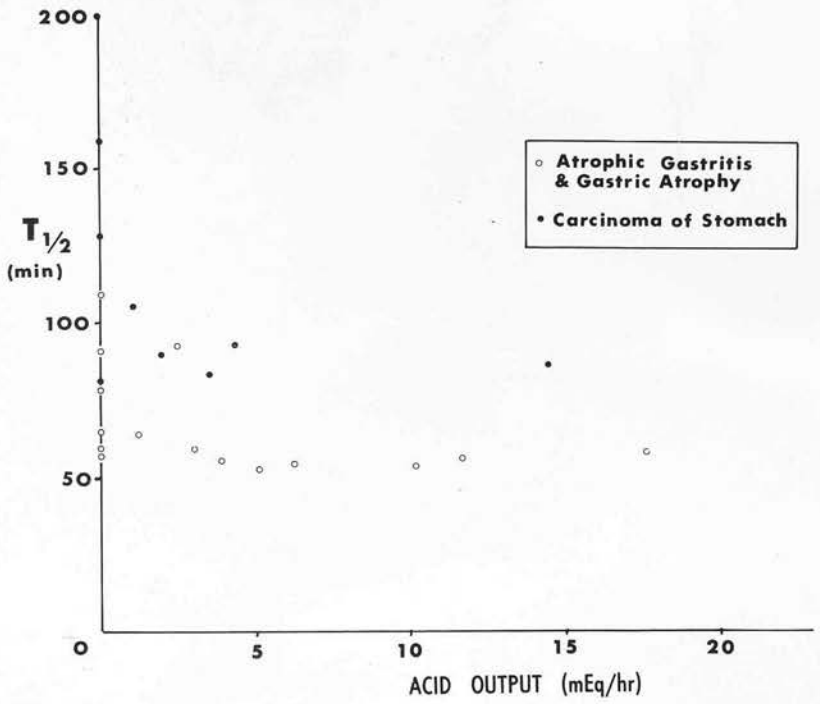


Figure 29: The relationship between the rate of gastric emptying and maximal acid output in subjects with atrophic gastritis and gastric carcinoma.

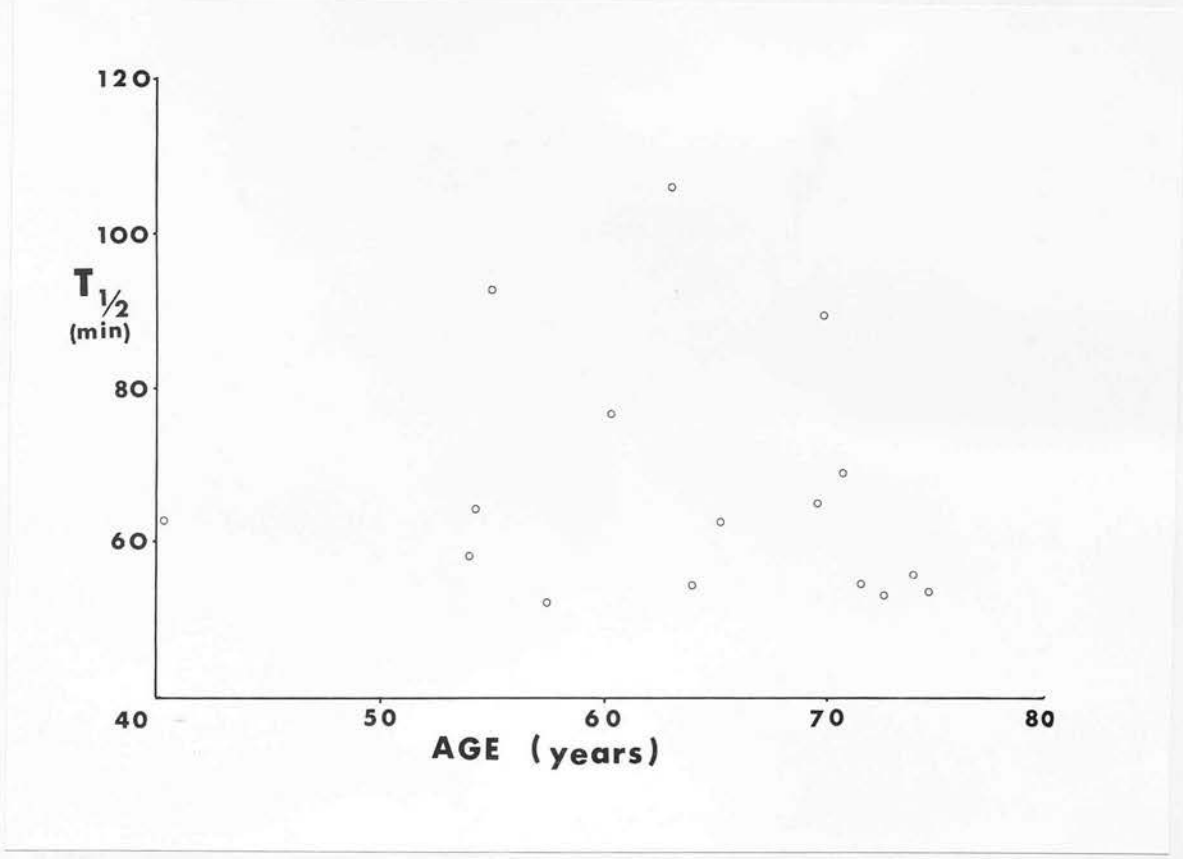


Figure 30: The relationship between the rate of gastric emptying and age in subjects with atrophic gastritis.

appear, therefore, that the significant difference between the emptying rate in the atrophic gastritis group and the contrast group is likely to be due to the existence of atrophic changes in the stomachs of the former group.

Animal experiments have demonstrated that the healthy gastric mucosa is resistant to the action of ingested carcinogen. If, however, a state of atrophic gastritis is first induced, the mucosa becomes more susceptible and Sommers (1958) has suggested that neoplasms tend to develop at sites of prolonged contact between carcinogen and abnormal mucosa. The cause of gastric cancer is unknown, but the evidence, such as it is, tends to incriminate dietary factors, at least in part (Boyd, Langman and Doll, 1964). The association between atrophic gastritis and intestinal metaplasia, and gastric cancer is well recognised and has already been discussed, as has the potential of intestinalised gastric epithelium to absorb ingested lipids. It may therefore be that the role of atrophic gastritis in the causation of gastric cancer is, in part, the associated delay in gastric emptying, allowing prolonged contact between dietary carcinogens and an atrophic and absorptive gastric epithelium.

It is of interest to note that, in patients with duodenal ulcer, the gastric emptying rate is rapid (Griffith, Owen, Campbell and Shields, 1968) and the incidence of gastric carcinoma extremely low.

CHAPTER 12

CONCLUSIONS

The results of the investigations which have been described may be considered in their application to the recognition of atrophic gastritis in three ways.

Firstly, they may be looked at from the standpoint of the value of each investigation in its ability to discriminate between non-atrophic and atrophic gastric mucosa. To this end a discriminatory index may be calculated as the number of cases in which the findings of the investigation in question agreed with the biopsy findings, expressed as a percentage of the total number examined (Table LXXXI). Such indices have been calculated for each investigation (Fig. 31) and it will be seen that the highest, and therefore most reliable, investigation was the measurement of gastric acid output when 10 mEq/hour was taken as the dividing line between atrophic and non-atrophic mucosa.

Secondly, the investigations may be compared by the frequency with which each correlated with the finding of atrophic gastritis, the higher the frequency, the fewer will be the 'false negative' results. Again, the measurement of gastric acid output was the most accurate, 79% of patients with atrophic gastritis having hypochlorhydria. Radiology and gastroscopy occupied an intermediate place with 56% and 54% respectively, while gastric photography proved to be a very unreliable method of detecting atrophic gastritis. The frequency of detection of the condition increased with its severity with all the methods which were studied. None of the haematological indices which were employed had a frequency higher than 31% (Fig. 32).

Lastly, the incidence of false-positive diagnosis is of importance in that it is an index of the reliability which can be ascribed to a finding. As will be seen from a study of Figures 5, 31 and 32, the false positive incidence in the clinical investigations was highest in the case of gastroscopy (14%) while acid output,

Findings on investigation	Biopsy: Atrophic	Biopsy: Non-atrophic	Total
Atrophic	a	b_1	$a + b_1$
Non-atrophic	a_1	b	$a_1 + b$
Total	$a + a_1$	$b + b_1$	$a + a_1 + b + b_1$

Discriminatory index	$\frac{a + b}{a + a_1 + b + b_1}$	x 100
Frequency of correlation with atrophic gastritis	$\frac{a}{a + a_1}$	x 100
False positive incidence for atrophic gastritis	$\frac{b_1}{b + b_1}$	x 100

Table LXXXI: The method of calculation of the discriminatory index, frequency of correlation, and false positive incidence of atrophic gastritis in the investigations employed.

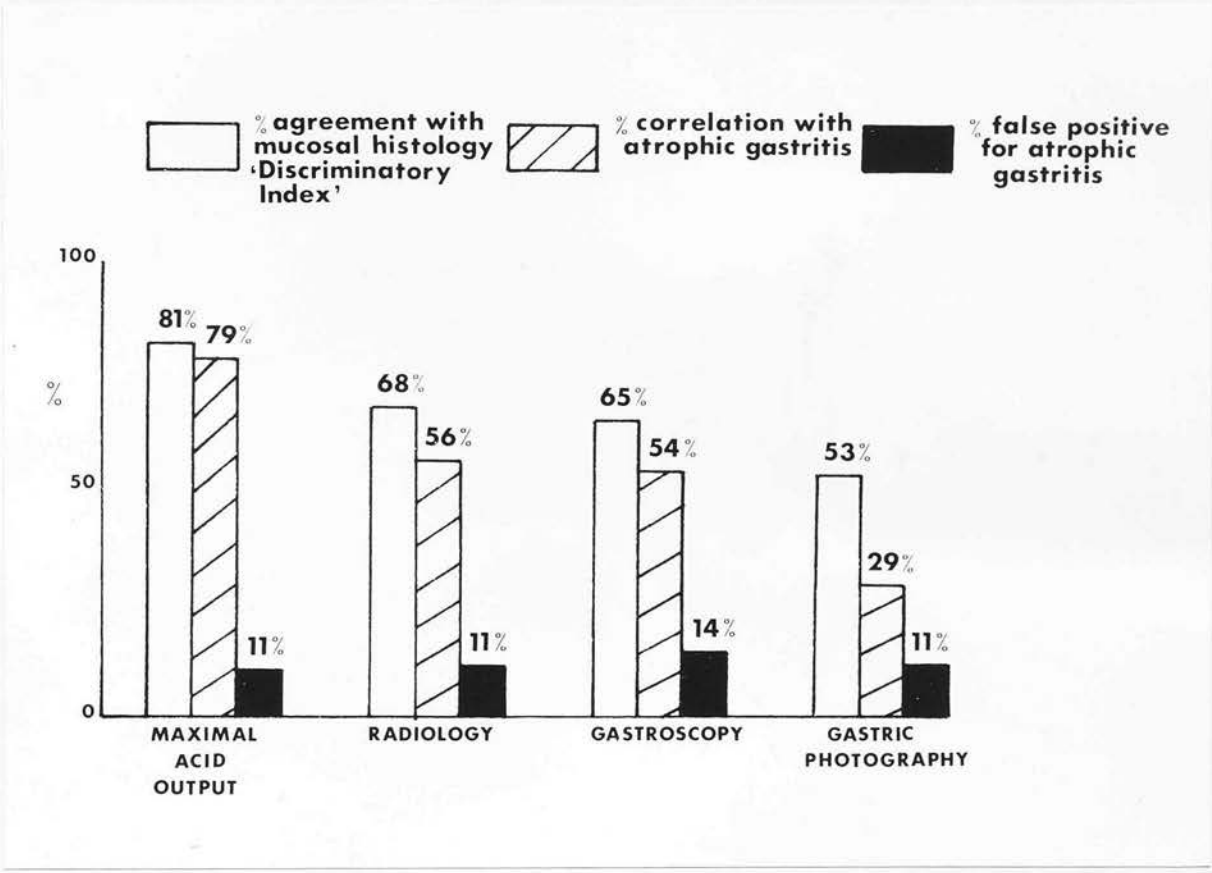


Figure 31: The 'discriminatory index', frequency of correlation with histological atrophic gastritis and incidence of false positive diagnosis of atrophic gastritis, in the clinical investigations under study.

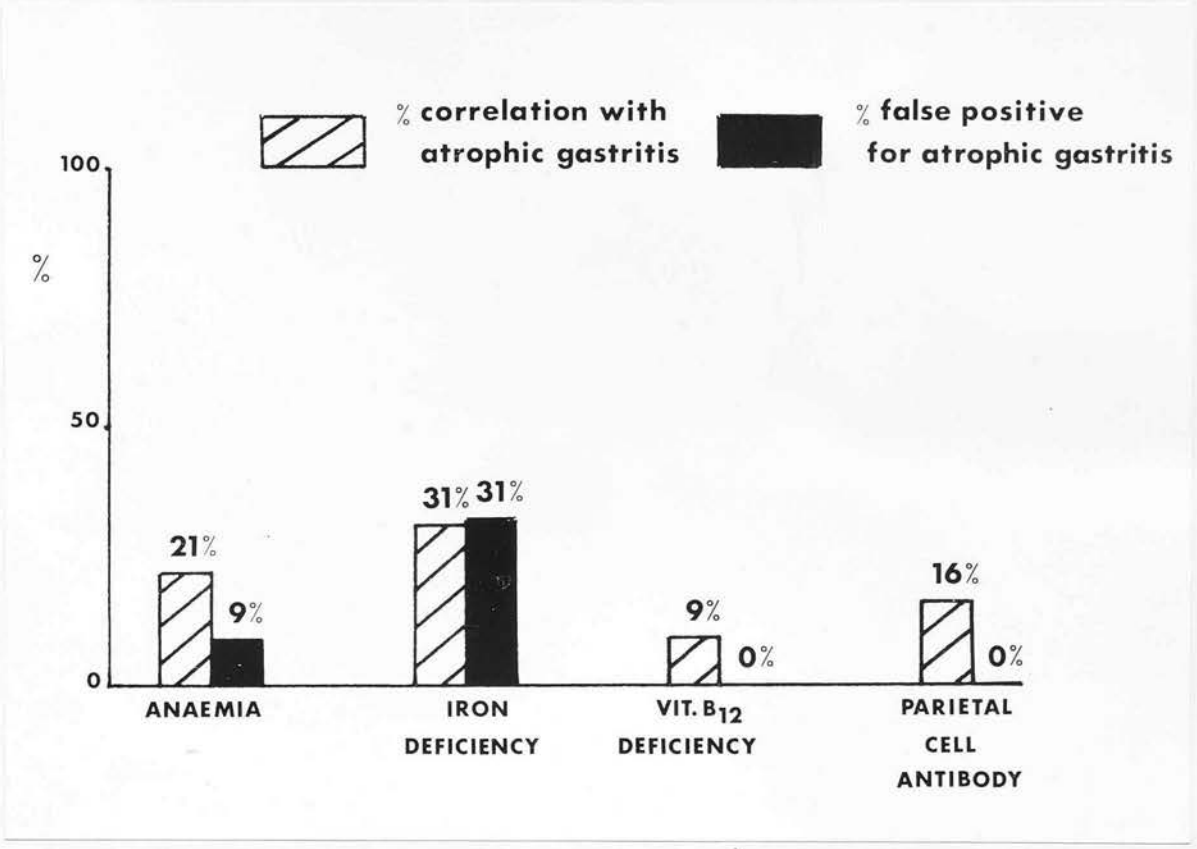


Figure 32: The percentage correlation with the presence of atrophic gastritis and the incidence of false positive 'diagnosis' of atrophic gastritis in four haematological parameters.

radiology and gastric photography all had a false-positive incidence of 11%. Iron deficiency was present in 31% of subjects with non-atrophic mucosa and in a similar percentage of those with atrophic gastritis and was thus valueless as an index of the state of the gastric mucosa. Vitamin B_{12} deficiency and the presence of parietal cell antibodies on the other hand, though low in incidence, had a false positive rate of nil.

When the findings of the investigations were combined, the combination of acid output, radiology, and gastroscopy and gastric photography, when compared with gastric biopsy findings in 88 subjects, resulted in an accuracy of recognition of atrophic gastritis of 84%, which was increased to 89% when the presence of Vitamin B_{12} deficiency and parietal cell antibodies were included. The false-positive incidence fell to 3% of 33 subjects with non-atrophic mucosa when the findings of the 4 clinical investigations were combined (Fig. 33).

It may be said, therefore, that, apart from iron deficiency, the incidence of false-positive findings from the investigations which have been described is low, especially when more than one investigation is carried out, and a finding suggestive of atrophic gastritis is highly likely to be correct.

The problem of the validity of gastric biopsy as being representative of the state of the gastric mucosa as a whole, has been discussed in an earlier chapter and commented upon in reviewing the results of certain of the investigations. An attempt has been made to assess this validity by comparing the findings on gastric biopsy with the results of the other investigations. This has not been without difficulty as every investigation was not performed upon every patient. Eighty-eight patients were available however upon whom

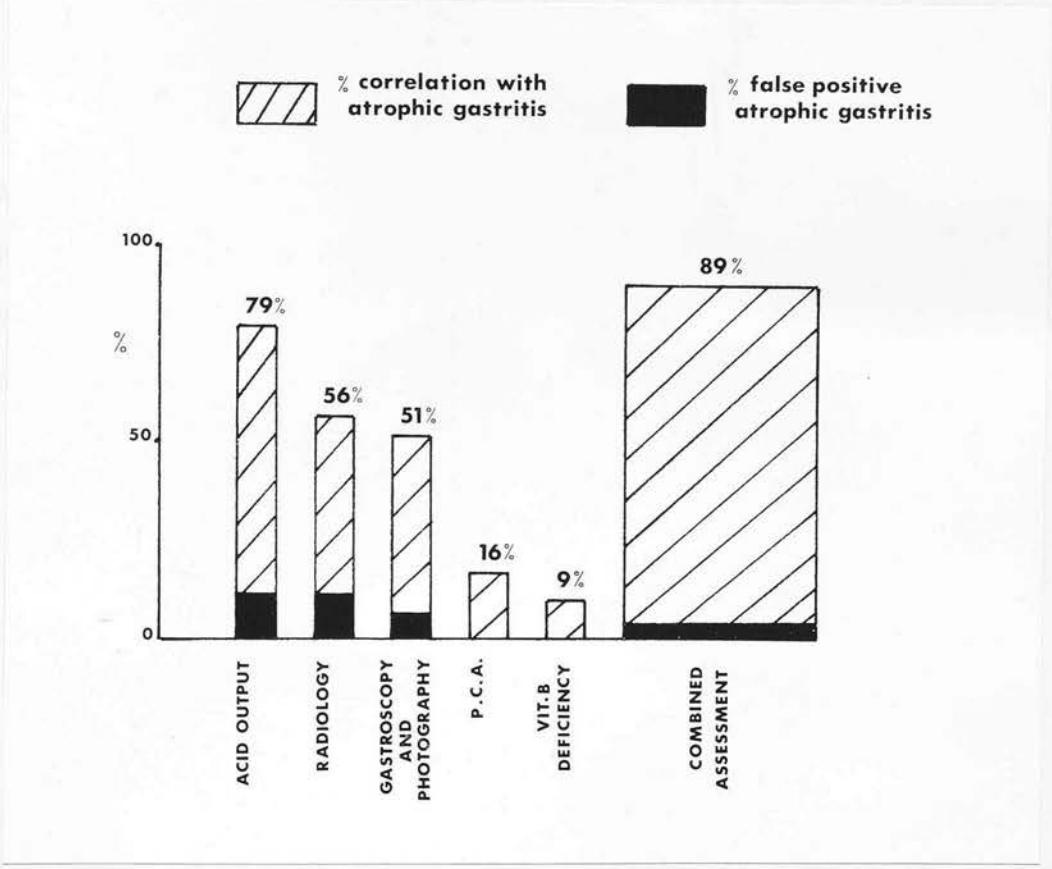


Figure 33: The percentage correlation with atrophic gastritis and incidence of false positive diagnosis in five investigations, individually and in combination.

gastric biopsy and maximal acid output estimation had been performed, and whose barium meal radiographs were available for scrutiny as to the presence or absence of the radiological signs of gastric atrophy. Complete agreement was found between these three parameters and with the findings on gastroscopy and gastric photography, where those had been carried out, in 47 (57%) of these subjects. Disagreement was found between the gastric biopsy findings and the interpretation of one or more investigations in the remaining 41 subjects. This was found in 24% of those with non-atrophic mucosa and in 34% of those with severe atrophic gastritis and gastric atrophy, and in 73% and 81% respectively of those subjects with mild or moderate degrees of atrophic gastritis. Of 33 subjects with non-atrophic mucosa, 4 (12%) were hypochlorhydric and 4 had radiological evidence of gastric atrophy; atrophic gastritis was considered to be present gastroscopically in 3 (18%) of those examined and in 1 (7%) by gastric photography. Of the 55 subjects with atrophic mucosa on biopsy, 13 (24%) had acid output levels above 10 mEq/hour, 24 (44%) had no radiological signs of gastric atrophy; 14 (47%) of those examined had no gastroscopic signs of atrophic gastritis, as had 14 (64%) of those upon whom gastric photography was carried out.

In order to test the validity of gastric biopsy in those cases where the findings differed, a point was given for each of three investigations. Where 2 points agreed, i.e. biopsy and acid output, biopsy and radiology, acid output and radiology, the biopsy was deemed valid or otherwise, and the results compared with such other findings as were available for corroboration, and a final assessment given. The details of the findings in these 41 subjects are shown in Table LXXXII. Of the 8 subjects with non-atrophic mucosa examined by this method, in 2 the biopsy was probably not representative of the

Biopsy	Acid output	Radiology	Gastroscopy	Photography	Comment	Final assessment
Non-atrophic	-	+	+	+		+
mucosa	+	-	+	+		+
"	+	+	-	+		+
"	+	+	+	-		+
"	+	-	0	+		+
"	-	+	-	0		+
"	-	-	-	+		-
"	-	-	0	0		-
Mild atrophic	+	-	-	+		+
gastritis	-	-	+	-		-
"	-	-	-	0		-
"	+	-	-	-	B_{12} deficient	+
"	+	+	+	-		+
"	-	-	+	0		-
"	-	-	0	-		-
"	-	-	0	0		-
Moderate	+	-	+	0		+
atrophic	-	-	-	0	B_{12} deficient	+
gastritis	-	-	+	0		-
"	-	-	-	0	P.C.A. present	+
"	-	-	-	0		-
"	+	-	-	0		+
"	+	-	+	-		+
"	+	-	-	-	P.C.A. present	+
"	+	+	-	0		+
"	-	-	0	0		-
"	-	-	-	0		-
"	+	+	-	0		+
"	-	-	0	0	P.C.A. present	+
"	-	+	0	-	P.C.A. present	+
"	+	+	-	0		+
"	+	-	0	0		+
"	+	+	0	-		+
Severe	+	-	0	+		+
atrophic	+	+	+	-		+
gastritis	+	-	+	-		+
and gastric	+	-	0	-	P.C.A. present	+
atrophy	+	+	+	-		+
"	+	+	0	0	B_{12} deficient	+
"	+	-	0	0		+
"	+	-	-	0		+

Table LXXXII: The findings in 41 subjects in whom agreement was not found between clinical investigations and gastric biopsy. Agreement with biopsy findings is signified by +, and disagreement by -.

mucosa as a whole, the weight of evidence being in favour of an atrophic mucosa. Of the 33 subjects with atrophic mucosa on biopsy, the evidence suggested a normal mucosa in 9. These were all subjects with mild or moderate degrees of atrophic gastritis and none had intestinal metaplasia. By thus comparing and correlating the investigative data, the gastric biopsy findings were corroborated in 77 (87.5%) of 88 subjects. Of the 11 in whom the weight of evidence was at variance with the biopsy findings 2, regarded as normal, could probably be properly designated as atrophic, and 9, hitherto regarded as atrophic, could be considered to have an essentially normal mucosa, the biopsies having sampled a portion of mucosa not representative of the whole. On this assumption, the accuracy of each investigation in discriminating between non-atrophic and atrophic gastric mucosa which has already been discussed, may be misleading and has been reassessed as shown in Figure 34.

The nature of atrophic gastritis has been discussed as has the evidence for the various aetiological factors involved in its pathogenesis. Its relationship to other disease processes has been reviewed and its importance as a clinical entity defined in particular relation to its potential as a precursor to gastric cancer and pernicious anaemia and its association with iron deficiency anaemia and non-ulcer dyspepsia.

A series of clinical and laboratory investigations has been performed on a group of dyspeptic patients and the results of these compared with the gastric biopsy findings with a view to evaluation of their usefulness in the recognition of atrophic gastritis. With regard to gastric biopsy itself, multiple biopsies were found to be similar in 91% of instances, suggesting that for routine practice a single biopsy is likely to be representative of the gastric mucosa

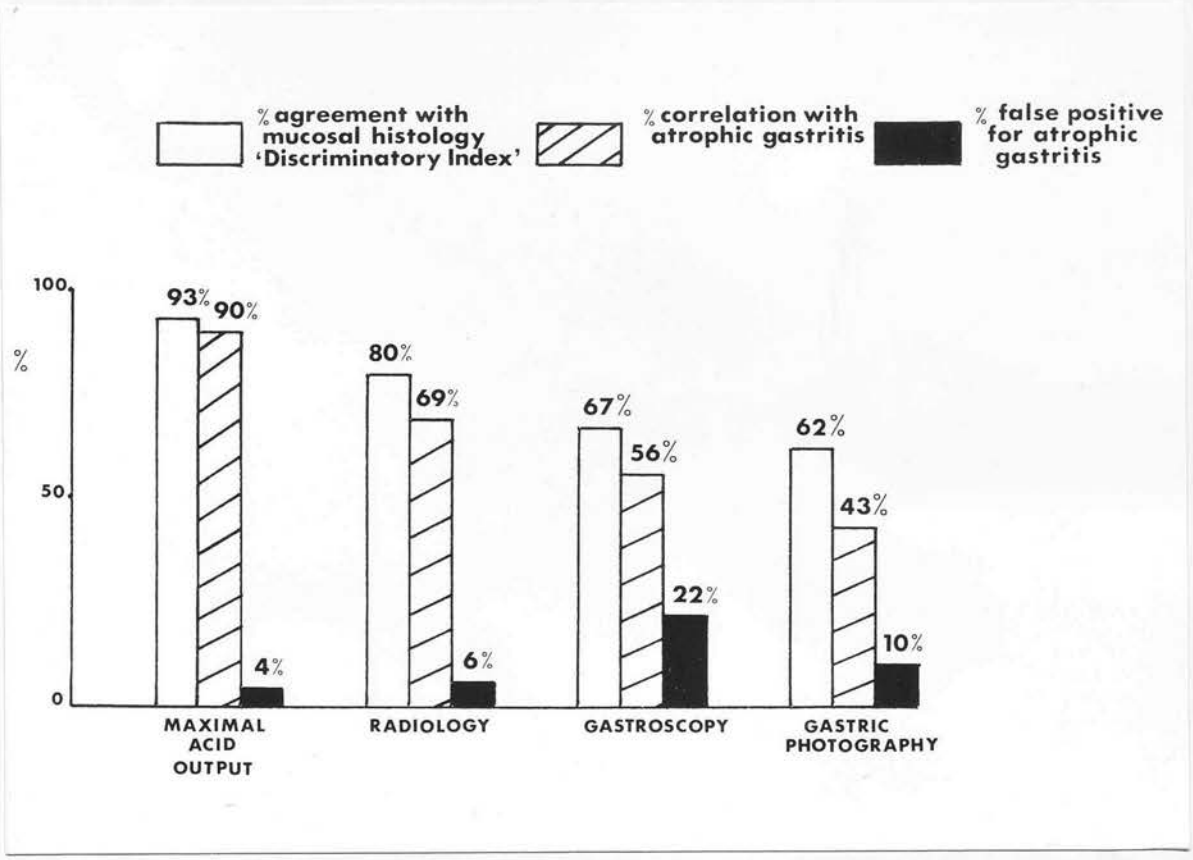


Figure 34: The 'discriminatory index', frequency of correlation with histological atrophic gastritis and incidence of false positive diagnosis in the clinical investigations after allowing for a sampling error of 13% in gastric biopsy

as a whole. A further significant finding was the presence of intestinal metaplasia in the gastric mucosa as a feature of all grades of severity of atrophic change, and not confined to those patients with severe atrophic gastritis. From the standpoint of the identification of patients with such a potentially pre-cancerous gastric mucosa, methods of recognition should therefore be capable of detecting the lesser, as well as the more severe, grades of the condition.

No valuable or significant clinical findings were found which were of assistance in recognising atrophic gastritis, but a significantly high proportion of subjects with this condition were found to have a family history of gastric carcinoma.

The estimation of maximal acid output was shown to be the most reliable index for the presence of atrophic change in the gastric mucosa. Careful study of barium meal radiographs was shown to be of substantial value in discriminating between atrophic and non-atrophic gastric mucosa, especially in the absence of focal gastric lesions, while gastroscopy and gastric photography were less reliable. The incidence of parietal cell antibodies in the group of subjects with atrophic gastritis was no higher than in the general population, and iron and Vitamin B_{12} deficiency were uncommon diagnostic features. When present, however, these haematological indices were valuable pointers towards the existence of atrophic gastritis. The incidence of false positive diagnoses by any of the investigations was low, and the finding of evidence suggestive of the existence of atrophic gastritis by any of the methods described is likely to be correct.

The reporting of a family history of gastric carcinoma or of pernicious anaemia, the presence of pernicious anaemia itself, the

finding of hypochlorhydria or of radiological or gastroscopic signs suggestive of gastric atrophic change, or the presence of parietal cell antibodies in the serum or of Vitamin B_{12} deficiency, are fairly frequent findings in routine clinical practice. Patients in whom these abnormalities are present have, or are likely to have, atrophic gastritis. They thus represent a population who may have an increased liability to develop gastric carcinoma, or to progress to pernicious anaemia. It is suggested that such patients should be subjected to gastric biopsy and, if atrophic gastritis is confirmed, they should be followed up by periodic haematological studies and by radiology or gastroscopy. It might, in addition, be of value to conduct a prospective study in detail of the dietary habits of such a group, in an endeavour to identify exogenous factors which might be associated with the development of gastric carcinoma.

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APPENDIX

Publications related to the subject matter of the thesis

Aubrey, D. A., Kirkpatrick, J. R. and Forrest, A. P. M. (1968) 'Gastric secretion in atrophic mucosal states' (Abstract of paper read to the Surgical Research Society) Brit. J. Surg., 55, 864

Davies, W. T., Kirkpatrick, J. R., Owen, G. M. and Shields, R. (1968) 'Alteration in the rate of gastric emptying as an aetiological factor in carcinoma of the stomach' (Abstract of paper read to the Surgical Research Society) Brit. J. Surg., 55, 866

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Forrest, A. P. M., Kirkpatrick, J. R., Lawrie, J. H., Gillespie, G., Gillespie, I. E., McCusker, V. I., Debas, H. T., Cox, A., Goudie, J. H., Spencer, J., Welbourn, R. B., Johnston, I. D. A., Spivery, J., Venables, C. W., Johnson, R. W. G., Boutchardt, E., Johnston, D., Jepson, K., Lari, J. and Duthie, H. L. (1969) 'Intramuscular pentagastrin compared with other stimuli as tests of gastric secretion: a multicentre study'. Lancet 1, 341-343.

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Davies, W. T., Kirkpatrick, J. R., Owen, G. M. and Shields, R. 'Gastric emptying in atrophic gastritis and carcinoma of the stomach' Scand. J. Gastroent. (In the press)

Table A: The results of the clinical investigations carried out upon the 115 patients included in the study. (The data have been tabulated according to sex and age in accordance with the findings on gastric biopsy. The results of barium meal examination, gastroscopy and gastric photography have been designated as showing, a normal appearance of the mucosa, 'N', an atrophic appearance, 'A', or no interpretation having been made, '-'. In the case of barium meal examination, the symbol '-' indicates that films were not available for retrospective scrutinty as discussed in Chapter 7. Where this symbol appears in the gastroscopy or gastric photography columns, it indicates that the examination was either not carried out or was unsatisfactory).

Name	Age	Diagnosis	Acid output	Ba. meal	Gastroscopy	Photography
NORMAL MUCOSA						
FEMALE:						
G.K.	55	G.U.	1.2	N	N	N
M.C.	56	N.U.D.	16.5	A	-	-
G.M.	59	D.U.	15.7	N	-	-
M.J.	66	N.U.D.	7.3	A	A	N
A.M.M.	67	N.U.D.	1.1	N	A	-
M.D.	71	N.U.D.	11.7	N	-	N
MALE:						
P.G.T.	42	D.U.	47.4	N	N	-
K.H.H.	43	N.U.D.	26.2	N	N	N
J.R.K.	44	D.U.	52.2	N	-	-
J.G.	46	D.U.	36.5	N	-	-
R.U.	47	D.U.	22.9	-	-	N
J.M.	49	N.U.D.	49.6	N	N	A
W.J.G.	50	D.U.	54.4	N	-	-
L.J.	53	D.U.	29.1	N	N	-
R.T.	54	G.U.	23.5	N	A	N
T.M.	54	N.U.D.	29.7	N	N	N
R.H.	57	D.U.	51.2	N	-	-
C.R.	57	N.U.D.	37.7	N	N	N
T.G.J.	58	N.U.D.	32.6	N	N	N
F.W.	64	D.U.	30.2	N	-	-
A.E.C.	65	D.U.	35.1	N	-	-
A.C.	66	D.U.	12.3	N	-	N
F.T.	69	D.U.	66.4	N	N	-
H.W.K.	70	D.U.	29.6	N	N	-
H.J.	71	N.U.D.	51.5	N	N	-
R.L.	75	Ca.	4.5	A	-	-
W.C.	77	G.U.	4.0	N	-	N
W.O.	77	N.U.D.	16.2	-	N	-

Name	Age	Diagnosis	Acid output	Ba. meal	Gastroscopy	Photography
SUPERFICIAL GASTRITIS						
FEMALE:						
M.T.	49	N.U.D.	3.1	-	-	-
E.P.	54	Ca.	40.6	-	-	N
MALE:						
T.G.J.	44	D.U.	61.4	N	-	-
C.B.	45	N.U.D.	26.8	-	-	N
W.G.	49	G.U.	23.3	N	N	-
R.H.	53	D.U.	37.1	-	-	N
G.J.R.	54	D.U.	13.7	N	-	-
G.R.D.	60	N.U.D.	11.6	N	N	-
C.E.C.	61	G.U.	24.8	-	N	-
P.C.	71	G.U.	12.3	A	-	N
G.W.	71	D.U.	33.2	N	-	-
J.L.Y.	73	N.U.D.	43.6	N	N	N
MILD ATROPHIC GASTRITIS						
FEMALE:						
L.P.	48	Ca.	8.4	-	-	N
A.P.	54	G.U.	6.0	A	-	-
O.H.	65	Ca.	3.9	N	-	-
A.H.	72	N.U.D.	9.8	A	A	A
H.L.	73	Ca.	7.6	A	-	-
M.L.	82	N.U.D.	1.1	A	A	N
MALE:						
D.M.	42	D.U.	35.2	N	-	-
K.F.	45	G.U.	9.9	N	N	A
W.H.	51	D.U.	20.7	-	-	N
G.T.	54	N.U.D.	18.6	N	A	-
W.E.K.	55	G.U.	24.7	N	N	-
R.R.	61	G.U.	29.7	-	-	-
F.L.D.	62	N.U.D.	7.7	-	N	N
T.M.	77	G.U.	15.1	N	A	N
A.H.	78	D.U.	34.2	N	-	-
MODERATE ATROPHIC GASTRITIS						
FEMALE:						
J.H.	40	N.U.D.	4.8	N	A	N
D.S.	57	N.U.D.	5.9	N	N	N
A.P.	60	N.U.D.	0.0	A	N	-
F.S.	60	N.U.D.	0.0	-	N	-
W.B.	64	G.U.	12.5	N	N	-
M.B.	69	P.A.	0.0	A	-	-
F.H.	69	Ca.	0.0	A	-	-
F.H.	73	Ca.	0.0	-	A	-
R.R.	76	Ca.	0.0	A	-	-
H.H.	77	Ca.	0.0	-	-	-

Name	Age	Diagnosis	Acid Output	Ba. meal	Gastroscopy	Photography
MODERATE ATROPHIC GASTRITIS						
MALE:						
J.B.	40	G.U.	4.1	N	A	-
R.D.	47	G.U.	7.6	N	N	-
J.D.C.	47	D.U.	37.8	N	N	-
G.P.	48	N.U.D.	1.1	-	N	N
R.W.	49	Ca.	9.7	N	A	-
G.E.	52	Ca.	16.1	A	-	N
K.C.R.	56	G.U.	18.0	N	N	-
W.A.L.	57	G.U.	11.2	N	A	-
F.G.C.	63	Ca.	0.0	A	N	-
J.W.W.	63	Ca.	0.0	N	-	-
I.T.W.	64	Ca.	2.4	A	-	-
R.J.S.	66	Ca.	14.6	N	-	-
J.C.S.	71	G.U.	19.6	N	N	-
E.J.P.	74	Ca.	0.0	A	N	-
V.B.	75	P.A.	0.0	A	-	N
W.G.T.	76	N.U.D.	0.0	-	-	-
SEVERE ATROPHIC GASTRITIS						
FEMALE:						
I.M.S.	40	N.U.D.	1.7	N	-	N
H.O.	51	Ca.	8.8	N	N	-
G.B.	54	N.U.D.	0.0	A	-	-
M.W.	62	N.U.D.	0.0	A	A	A
F.A.	63	N.U.D.	3.9	N	-	N
F.H.	65	N.U.D.	6.4	A	-	N
E.G.	71	G.U.	2.9	A	A	-
M.L.	73	N.U.D.	2.2	N	-	-
J.C.	73	N.U.D.	0.0	A	N	N
L.O.	73	N.U.D.	0.0	N	A	N
V.W.	74	N.U.D.	0.0	A	-	A
M.L.	77	D.U.	3.1	A	-	-
MALE:						
T.V.	40	N.U.D.	0.0	A	A	N
G.W.	46	N.U.D.	0.0	A	A	N
J.S.	49	N.U.D.	0.0	-	-	-
B.C.C.	49	G.U.	40.6	-	-	N
C.H.J.	52	Ca.	0.0	A	-	-
L.B.D.	53	P.A.	0.0	-	-	-
D.D.	54	P.A.	0.0	A	-	A
L.S.	54	N.U.D.	2.6	A	A	-
S.N.	61	G.U.	0.0	-	A	N
F.S.	62	N.U.D.	0.0	A	A	A
M.W.	64	Ca.	0.0	-	-	-
G.P.	66	P.A.	0.0	A	A	A
N.A.G.	68	G.U.	4.8	A	A	-
D.J.	74	N.U.D.	5.3	A	-	A

Name	Age	Diagnosis	Acid output	Ba. meal	Gastroscopy	Photography
GASTRIC ATROPHY						
FEMALE:						
F.P.	67	P.A.	0.0	A	-	-
A.M.J.	69	P.A.	0.0	-	-	N
MALE:						
L.L.	70	P.A.	0.0	-	-	-
J.S.	71	P.A.	0.0	A	-	-
NO BIOPSY TAKEN						
FEMALE:						
L.C.G.	74	Ca.	6.0	A	-	-
MALE:						
G.H.D.	58	Ca.	1.1	A	-	-
A.R.	69	Ca.	0.0	N	-	-
J.W.	73	Ca.	0.0	A	-	-

Table B: The results of the haematological investigations carried out on the 115 patients included in the study. (The data have been tabulated according to sex and age in accordance with the findings on gastric biopsy. The haematological values in brackets are those of patients with pernicious anaemia under treatment at the time of the study. The symbol * indicates that parietal cell antibodies were found in the serum, and the symbol ** indicates that intrinsic factor antibody was found in addition).

Name	Age	Diagnosis	Hb.	MCHC	MCV	Fe.	TIBC	B_{12}	Group	FOB
NORMAL MUCOSA										
FEMALE:										
G.K.	55	G.U.	13.9	34	89	85	400	317	0	-
M.C.	56	N.U.D.	12.8	33	90	50	375	320	B	-
G.M.	59	D.U.	13.4	33	90	100	360	460	0	-
M.J.	66	N.U.D.	14.4	33	105	145	330	200	A	-
A.M.M.	67	N.U.D.	14.4	33	82	120	345	236	A	-
M.D.	71	N.U.D.	11.7	32	102	65	330	516	B	-
MALE:										
P.G.T.	42	D.U.	15.7	33	90	190	360	306	A	-
K.H.H.	43	N.U.D.	14.8	32	82	100	285	149	0	-
J.R.K.	44	D.U.	17.0	35	83	95	450	259	0	-
J.G.	46	D.U.	15.4	35	90	75	480	412	0	+
R.U.	47	D.U.	14.9	33	87	25	300	377	A	-
J.M.	49	N.U.D.	16.0	35	83	165	450	206		-
W.J.G.	50	D.U.	16.3	33	102	130	300	188	A	-
L.J.	53	D.U.	16.8	35	83	100	375	358	0	-
R.T.	54	G.U.	14.2	33	86	80	390	300	0	-
T.M.	54	N.U.D.	13.9	35	100	110	270	177	0	-
R.H.	57	D.U.	16.0	36	93	100	390	266	0	-
C.R.	57	N.U.D.	14.9	33	84	100	360	356	A	-
T.G.J.	58	N.U.D.	14.2	34	92	55	315	264	A	-
F.W.	64	D.U.	15.4	36	100	50	390	722	B	-
A.E.C.	65	D.U.	13.8	32	88	65	255	253	0	-
A.C.	66	D.U.	15.8	34	93	135	390	334	0	-
F.T.	69	D.U.	11.3	32	83	50	360	331	B	+
H.W.K.	70	D.U.	13.9	34	81	95	330	154	0	-
H.J.	71	N.U.D.	15.7	34	90	175	375	225	A	-
R.L.	75	Ca.	12.4	32	84	75	345	373	A	+
W.C.	77	G.U.	14.5	36	80	95	330	207	0	-
W.O.	77	N.U.D.	15.7	33	94	140	345	236	A	-
SUPERFICIAL GASTRITIS										
FEMALE:										
M.T.	49	N.U.D.	13.0	30	93	50	405	456	0	-
E.P.	54	Ca.	13.1	32	87	165	795	355	A	-

Name	Age	Diagnosis	Hb.	MCHC	MCV	Fe.	TIBC	B_{12}	Group	F.O.B.
SUPERFICIAL GASTRITIS										
MALE:										
T.G.J.	44	D.U.	17.0	33	86	115	360	283	A	-
C.B.	45	N.U.D.	16.8	35	90	125	405	139	O	-
W.G.	49	G.U.	16.6	33	100	125	420	188	O	-
R.H.	53	D.U.	14.8	32	88	105	390	307	B	-
G.J.R.	54	D.U.	15.8	34	88	125	405	503	O	-
G.R.D.	60	N.U.D.	17.4	34	82	125	300	486	O	-
C.E.C.	61	G.U.	17.1	35	85	220	435	236	AB	-
P.C.	71	G.U.	16.7	30	91	140	375	312	O	-
G.W.	71	D.U.	11.3	31	85	50	270	445	O	+
J.L.Y.	73	N.U.D.	16.3	34	90	95	375	349	A	-
MILD ATROPHIC GASTRITIS										
FEMALE:										
L.P.	48	Ca.	14.1	32	82	85	540	363	O	-
A.P.*	54	G.U.	13.9	33	89	45	270		A	-
O.H.	65	Ca.	8.6	29	93	70	255	143	O	+
A.H.	72	N.U.D.	13.6	33	90	125	330	254	O	-
H.L.*	73	Ca.	9.2	30	72	40	510	94	O	+
M.L.	82	N.U.D.	12.4	33	88	55	360	321	O	-
MALE:										
D.M.	42	D.U.	16.1	33	76	110	465	305	O	-
K.F.	45	G.U.	15.7	34	85	85	390	331	A	-
W.H.	51	D.U.	18.4	36	100	80	435	500	AB	+
G.T.	54	N.U.D.	16.6	33	90	85	420	178	O	-
W.E.K.	55	G.U.	15.5	34	79	130	375	373	O	-
R.R.	61	G.U.	14.9	32	82	105	420	223	A	-
F.L.D.	62	N.U.D.	15.8	33	104	75	270	101	O	-
T.M.	77	G.U.	13.9	34	83	115	345	472	A	+
A.H.	78	D.U.	12.0	32	97	35	400	400	O	-
MODERATE ATROPHIC GASTRITIS										
FEMALE:										
J.H.	40	N.U.D.	14.1	34	93	95	360	221	O	-
D.S.*	57	N.U.D.	14.8	34	100	105	435	204	O	-
A.P.	60	N.U.D.	13.1	32	77	160	420	231	A	-
F.S.**	60	N.U.D.	13.9	35	82	120	375	206	B	-
W.B.*	64	G.U.	15.7	34	80	160	420	163	O	-
M.B.**	69	P.A.	(12.7	33	103	125	420	)	B	-
F.H.	69	Ca.	8.9	29	66	30	375		A	+
F.H.	73	Ca.	12.6	31	80	50	495	241	A	+
R.R.	76	Ca.	10.4	33	76	42	432		A	+
H.H.	77	Ca.	12.7	31	80				B	-

Name	Age	Diagnosis	Hb.	MCHC	MCV	Fe.	TIBC	B_{12}	Group	FOB
MODERATE ATROPHIC GASTRITIS										
MALE:										
J.B.	40	G.U.	16.4	35	86	210	465	268	O	-
R.D.	47	G.U.	3.7	21	68	25	345	193	O	+
J.D.C.	47	D.U.	15.4	33	83	215	300	292	A	-
G.P.	48	N.U.D.	16.0	36	90	150	225	143	A	-
R.W.	49	Ca.	13.5	34	79	90	405	322	O	-
G.E.	52	Ca.	15.7	31	84	75	390	196	A	-
K.C.R.	56	G.U.	14.8	32	92	115	330	125	A	-
W.A.L.	57	G.U.	15.7	34	102	150	510	351	O	-
F.G.C.	63	Ca.	7.8	26	65	75	525		O	+
J.W.M.	63	Ca.	15.8	32	85	45	315	320	O	+
I.T.W.	64	Ca.	8.9	27	75	40	300	256	O	+
R.J.S.*	66	Ca.	16.4	34	78	100	330	279	O	-
J.C.S.	71	G.U.	15.2	33	95	110	340	106	O	-
E.J.P.	74	Ca.	7.5	29	79	10	411	323	A	+
V.B.	75	P.A.	9.6	32	96	190	330	70	A	-
W.G.T.	76	N.U.D.	12.6	33	84	165	345	135	A	-
SEVERE ATROPHIC GASTRITIS										
FEMALE:										
I.M.S.	40	N.U.D.	8.9	30	74	150	450	355	A	-
H.O.	51	Ca.	15.1	34	73	25	375	249	O	-
G.B.	54	N.U.D.	5.8	22	84	20	660	632	A	-
M.W.*	62	N.U.D.	10.5	30	84	35	510	211	A	-
F.A.*	63	N.U.D.	15.7	34	95	145	420	386	A	-
F.H.	65	N.U.D.	13.6	32	97	165	360	159	O	-
E.G.	71	G.U.	13.5	36	77	86	375	148	B	-
M.L.	73	N.U.D.	6.0	29	80	30	600	264	A	-
J.C.	73	N.U.D.	14.5	33	86	75	390	72	O	-
L.O.	73	N.U.D.	13.1	34	97	150	315	206	A	-
V.W.	74	N.U.D.	14.8	35	85	80	345	262	AB	-
M.L.	77	D.U.	11.7	29	80	35	195	388	O	-
MALE:										
T.V.	40	N.U.D.	15.7	34	83	130	330	129	O	-
G.W.	46	N.U.D.	14.8	34	104	145	400	132	O	-
J.S.*	49	N.U.D.	15.2	33	95	180	435	102	A	-
B.C.C.	49	G.U.	15.1	30	102	50	375	407	B	+
C.H.J.	52	Ca.	12.4	31	79	45	285	533	AB	-
L.B.D.*	53	P.A.	6.9	36	100	175	330	29	AB	-
D.D.*	54	P.A.	12.7	34	97	100	240	46	A	-
L.S.	54	N.U.D.	14.9	35	83	135	300	212	A	-
S.N.	61	G.U.	9.2	29	71	30	570	364	O	+
F.S.*	62	N.U.D.	16.3	35	97	130	300	98	O	-
M.W.	64	Ca.	17.6	33	96	75	470	470	O	-
G.P.*	66	P.A.	6.0	33	112	185	285	17	A	-
N.A.G.	68	G.U.	15.5	32	97	135	420	220	O	-
D.J.	74	N.U.D.	9.5	31	111	115	330	135	A	-

Name	Age	Diagnosis	Hb.	MCHC	MCV	Fe.	TIBC	B_{12}	Group	FOB
GASTRIC ATROPHY										
FEMALE:										
F.P.	67	P.A.	4.7	31	93	120	270	77	A	-
A.M.J.**	69	P.A.	(12.5	33	103	135	480	)		-
MALE:										
L.L.*	70	P.A.	(13.5	32	89	95	420	)	A	-
J.S.	71	P.A.	7.4	29	108	125	345	80	A	-
NO BIOPSY TAKEN										
FEMALE:										
L.C.G.	74	Ca.	7.5	27	73	55	405	242	A	-
MALE:										
G.H.D.	58	Ca.	8.9	27	70	70	405	266	A	+
A.R.	69	Ca.	4.7	24	69	40	360	102	O	+
J.W.	73	Ca.	9.9	32	81	105	240	504	O	+

ACID OUTPUT

SUBJECT	HISTAMINE INFUSION 40 ug/kg/hr							PENTAGASTRIN I.M. 6 ug/kg		
	0-15 min (mEq)	15-30 min (mEq)	30-45 min (mEq)	45-60 min (mEq)	60-75 min (mEq)	75-90 min (mEq)	Peak hour (mEq/hr.)	0-10 min (mEq)	10-30 min (mEq)	10-30 min x 3 (mEq/hr)
G.P.	Nil	Nil	0.17	0.22	0.70	0.64	1.73	Nil	0.36	1.08
H.T.R.	3.57	8.51	8.38	9.12	8.73		34.74	0.56	8.93	26.79
J.D.	5.25	6.98	8.81	8.49	9.34	8.66	35.30	2.56	8.64	25.92
C.F.	5.56	7.70	7.63	8.06	8.71	8.51	32.91	2.48	9.49	28.47
J.E.L.	3.26	7.37	7.02	8.36	9.43	10.10	34.91	2.60	8.19	24.57
A.P.	2.92	9.08	13.42	9.03	23.20		54.73	2.36	19.90	59.70
J.R.B.	Nil	Nil	Nil	0.27	0.31		1.16	Nil	1.34	4.02
T.V.	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
A.F.	Nil	2.12	2.39	2.44	2.62	2.04	9.45	Nil	3.19	9.57
A.V.	3.12	6.03	5.58	6.49	7.18		25.28	3.66	7.92	23.76
M.J.	0.74	2.16	3.30	4.09	2.51	3.10	13.09	0.29	2.42	7.26
A.H.	Nil	1.86	2.52	2.35	3.23		9.96	0.65	4.46	13.38
J.R.	4.46	9.92	10.10	9.96	10.56	10.67	41.40	3.60	13.70	41.10
J.G.	5.60	10.41	9.15	10.53	10.40		40.79	4.69	12.18	36.54
B.B.	5.09	9.44	10.17	10.76	11.18	11.30	43.40	4.32	7.32	21.96
D.H.	8.64	11.68	13.03	14.58	7.44		46.73	1.91	12.37	37.11
G.T.	0.38	2.52	2.65	3.20	2.77	3.06	11.68	0.94	4.89	14.67
D.E.	4.45	7.44	7.38	10.91	7.96	7.35	33.60	1.87	6.55	19.65
F.P.	Nil	2.34	2.11	2.84	2.70	2.86	10.51	Nil	1.64	4.92
W.R.	5.52	6.71	5.17	6.60	6.96		25.40	2.15	9.40	28.20
H.K.	2.41	2.61	3.33	3.68	3.29	4.03	14.33	0.39	2.34	7.02
A.C.	5.14	7.80	10.37	8.77	6.02		32.96	4.45	11.70	35.10
G.B.	Nil	Nil	Nil	Nil	Nil		Nil	Nil	Nil	Nil
G.W.	Nil	Nil	Nil	Nil	Nil		Nil	Nil	Nil	Nil
P.G.T.	1.28	2.48	3.23	6.71	6.44	2.54	18.92	2.78	15.80	47.40
J.G.	3.68	15.35	12.93	14.80	10.70	16.0	54.48	6.20	16.63	49.89
						Mean 24.17 ± S.E.3.42			Mean 21.84 ± S.E. 3.33	

Table C: The output of gastric acid obtained in response to histamine acid phosphate by intravenous infusion, 40 ug/kg/hour, and to pentagastrin intramuscularly, 6 ug/kg., in 26 subjects.

ACID OUTPUT

SUBJECT	HISTAMINE S.C. 40 ug/kg							PENTAGASTRIN I.M. 6 ug/kg		
	0-10 min (mEq)	10-20 min (mEq)	20-30 min (mEq)	30-40 min (mEq)	40-50 min (mEq)	50-60 min (mEq)	Peak 30 min x 2 (mEq/hr.)	0-10 min (mEq)	10-30 min (mEq)	10-30 min x 3 (mEq/hr)
J.E.J.	1.28	4.31	3.40	4.11	3.55	2.92	23.64	0.44	4.70	14.10
A.D.	1.97	1.78	0.82	1.63	3.37	2.56	15.13	0.98	5.63	16.89
A.P.	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
M.J.W.	8.19	10.32	10.22	11.64	10.76	10.69	66.18	3.60	21.81	65.43
R.E.	2.29	6.25	6.29	9.14	6.63	8.45	48.44	3.06	16.05	48.15
J.C.	0.45	2.76	3.49	4.86	3.81	4.18	25.70	2.55	12.60	37.80
P.C.	Nil	1.43	1.57	1.89	2.31	2.91	14.22	Nil	4.07	12.21
G.E.	Nil	1.20	1.02	1.67	1.95	2.01	11.26	1.29	5.38	16.14
G.M.M.	Nil	0.67	2.40	2.27	3.79	2.88	17.88	0.24	6.20	18.60
C.D.	4.09	5.61	5.38	6.56	4.84	4.59	35.10	3.27	13.45	40.35
C.E.C.	0.87	3.28	4.10	3.99	4.18	4.92	26.18	1.53	8.27	24.81
A.J.P.	Nil	1.55	2.46	2.35	2.73	2.37	14.93	2.73	5.82	17.46
T.M.	1.90	4.18	2.91	5.95	5.56	5.16	33.36	2.61	11.43	34.29
H.W.K.	2.21	3.25	3.86	4.49	3.85	3.53	24.40	1.41	9.88	29.64
B.M.D.	0.43	2.57	3.57	4.34	3.88	4.75	25.94	0.31	7.65	22.95
R.R.	7.10	4.45	5.40	4.50	4.62	3.77	29.04	2.94	9.91	29.73
R.M.	0.33	2.88	4.31	4.34	4.46	4.17	26.22	1.62	8.17	24.51
C.R.	4.17	6.02	6.62	6.12	6.48	6.96	39.12	4.29	12.55	37.65
P.H.	2.65	3.63	7.42	5.63	7.13	5.35	40.36	0.42	12.86	38.58
W.R.K.	1.29	3.78	3.74	4.14	4.60	4.20	25.88	0.89	8.25	24.75
D.M.	1.50	3.23	3.69	5.41	4.06	4.57	28.08	0.33	11.77	35.20
A.O.	2.55	8.39	5.72	5.99	6.99	6.94	40.20	3.87	12.59	37.77
I.H.	3.43	6.85	7.44	7.83	7.75	6.53	46.04	3.45	16.98	50.94
J.R.K.	9.30	12.10	12.70	13.30	12.0	13.10	45.78	3.16	17.42	52.26
A.C.	2.55	8.39	5.72	5.99	6.99	6.94	40.20	3.87	12.59	37.77
						Mean	29.73		Mean	30.72
						± S.E.	2.84		± S.E.	2.95

Table D: The output of gastric acid obtained in response to histamine acid phosphate subcutaneously 40 ug/kg, and to pentagastrin intramuscularly, 6 ug/kg., in 25 subjects.